JUL 19 1918
UNIV. OF MICH.
LIBRARY

VOLUME 22 NUMBER 1

THE ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston LOUIS V. HARRMAN, Baltimore

GEORGE BLOCK, St. Louis MARFIELD T. CONGDON, New York

W. S. THAYER, Baltimore

JULY 15, 1918

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 22, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 15, 1918.

CONTENTS OF VOLUME XXI

JANUARY, 1918. NUMBER 1

The Value of the Atropin Test in the Diagnosis of Typhoid Fever. Edward M. Brown, M.D., Montreal, Quebec.

Factors in Resistance to Tuberculosis. Alfred F. Petersen, M.D., Chicago.

Lipothymia Progressiva. Irving J. Sands, M.D., Baltimore.

The Effect of Various Neutral Solutions on Gastric Discharge, Gastric Secretion and Duodenal Regurgitation. W. E. Meyer, A.B., M.D., Chicago.

A Simple Technic for the Demonstration of a Phagocytic Mononuclear Cell in Peripheral Blood. First Report of Studies on the Mononuclear Cells of the Blood. F. A. McJunkin, M.D., Milwaukee.

Calcification in the Pineal Gland. Ralph B. Rose, M.D., and Thomas Schoolcraft, M.D., New York.

Anatomic Observations Concerning the Mechanism of Bile Resorption in Jaundice. Ernst Gertel, M.D., Montreal, Quebec.

The Effect of Diet on Blood Sugar in Diabetes Mellitus. Herman O. Mosenthal, M.D., Russell W. Clausen, M.D., and Alan Mayer, M.D.S., Baltimore.

Studies on the Bifurcation in Cattle. Leo Wentworth, M.D., and Cecil McClure, M.D., Boston.

Stimulation of the Respiration by Sodium Cyanid and Its Clinical Application. A. S. Loevenhart, M.D., W. J. Lorenz, M.D., H. C. Martin, M.D., and J. V. Mathis, M.D., Madison, Wis.

The Influence of Large Doses of Thyroid Extract on the Fetal Thyroid and Hypophysis in a Case of Hyperemesis. J. C. Ash, M.D., and M. S. Sloan, M.D., Boston.

Extensive Calcification of the Tissues as a Result of Disease. Jeanne Hertha, M.D., Christiania, Norway.

Auricular Flutter. John M. Blackford, M.D., Seattle, and Fred R. White, M.D., Rochester, Minn.

Heart Block. I. Two Cases of Complete Heart Block Showing Ventricular Pseudo-rhythm. Fred R. White, M.D., and C. Canby Robinson, M.D., St. Louis.

The Rate of Absorption and Elimination of the Ions of Strontium, Sodium and Potassium. A. J. Rychlik, M.D., Omaha, and J. P. Fischer, M.D., Cleveland.

FEBRUARY, 1918. NUMBER 2

Thyroid-Blocks IV. Transmit Specificity. Blocks with Mammary Secretion. Joseph Bamberger, M.D., Frank N. Wilson, M.D., and G. Canby Robinson, M.D., St. Louis.

The Endocrine Origin of Muscular Dystrophy. N. W. Janney, M.D., S. P. Goodhart, M.D., and V. I. Isaacson, B.S., New York.

Studies in Acute Nephritis. Edward H. Mason, M.D., Montreal, Quebec.

A Papillary Carcinoma of the Kidney with Metastasis in the Brain. Edwin F. Hirsch, M.D., Chicago.

The Relationship of the Toxic Lymphoid Hyperplasias to Lymphosarcoma and Allied Diseases. Douglas Symmers, M.D., New York.

The Nature of the Pathologic Process in Progressive Muscular Dystrophy. E. A. McCulloch, M.D., Boston.

Chemical Changes in the Blood and Urine in Progressive Muscular Dystrophy, Myasthenia, Muscular Atrophy and Myasthenia Gravis. F. H. MacKaye, M.D., and C. S. Sargent, S.B., Boston.

The Effect of Thyroid Secretion on the Excitability of the Rhythm of the Cardiac Ventricle. Robert L. Levy, M.D., Baltimore.

The Maintenance Diet in Diabetes Mellitus as Determined by the Nitrogen Equilibrium. Herman O. Mosenthal, M.D., and Samuel W. Clausen, M.D., Baltimore.

The Distribution of Bile in Certain Types of Jaundice. E. A. Bloomfield, M.D., Cleveland.

Experimental Intestinal Obstruction. Frank C. Smith, B.S., M.D., and Leo J. Hauck, M.S., M.D., Chicago.

MARCH, 1918. NUMBER 3

A New Remedy, Myrtol, Especially Its Use in Syphilis Larvata. Maurice C. Hall, Ph.D., Detroit.

A Comparison of the Functional and Anatomic Findings in a Series of Cases of Arterial Disease. A. Steiegel, M.D., J. H. Austin, M.D., and L. Jones, M.D., Philadelphia.

The Relationship of the So-Called Idiopathic Cardiopathy to Exophthalmic Goiter. D. Summers, M.D., New York.

The Effect of Digestion on the General Blood Pressure in Animals with Consideration of the Renal Arteries. E. W. Bridgman, M.D., Baltimore, and K. Hirose, M.D., Okayama, Japan.

Influence of Extrarenal Factors on the Renal Functional Test Meal. G. G. Lyle, M.D., and H. Sharlit, M.D., New York.

Contributions to the Physiology of the Stomach. XLVI. Gastric Secretion During Fever. J. Meyer, M.D., A. J. Carlson, Ph.D., and A. J. Carlson, Ph.D., Chicago.

A Study of Paroxysmal Tachycardia with Especial Reference to Tachycardia of Ventricular Origin. W. S. Thayer, M.D., Boston.

Pharmacodynamic Examination of the Vasomotor Nervous System in Syphilis Fever. A Contribution to the Problem of Bradypnea. L. Mariano, M.D., and T. Morikami, M.D., Kioto, Japan.

The Action of Tyramin on the Circulation of Man. A. W. Hewlett, M.D., San Francisco.

Observations Regarding the Loss of Water Vapor Through the Skin of Infants. W. McClure, M.D., and L. M. Sloan, M.D., Chicago.

The Archives of Internal Medicine

Vol. XXII JULY, 1918 No. 1

THE BLOOD IN SHOCK*

C. C. GUTHRIE, M.D.

INTRODUCTION

It has been stated that in shock liquid passes from the blood to the tissues,[1] resulting in alterations of physical condition, as increased specific gravity, red cell count, viscosity, and decrease in total blood volume.

In an investigation of experimental shock in dogs,[2] the blood was studied to determine if such alterations occurred in the type of shock induced, and if there was a causal relation between blood change and shock.

METHODS AND RESULTS

Dogs under ether anesthesia were reduced to a state of shock, essentially by nerve stimulation.[3] Some blood was lost by operative procedures and by taking samples for analyses, but in no case was such loss in itself of sufficient magnitude to induce shock. In typical cases the blood pressure was greatly lowered, the cardiac output was decreased—as indicated by diminished pulse pressure and volume—respiration was irregular, eye reflexes were present and slight if any tendency to recover was manifested on discontinuing the administration of ether. Alterations in reflex vasomotor phenomena were marked. Great differences in susceptibility to shock were exhibited by different dogs. Arterial blood samples were taken before and after shock. Coagulation was prevented by defibrination, and to control the findings a few samples were prevented from coagulating by the addition of potassium oxalate.

Specific gravity was determined by weighing. It moderately and progressively decreased. Taking into account the relatively high specific gravity of red blood corpuscles, it would seem that the reduction in the specific gravity of the blood was largely due to the dilution of the corpuscles from increase of plasma volume.

Hematokrit tests and *red cell counts* were performed in the usual manner. The volume per cent. of red corpuscles and the number per unit of blood progressively decreased, indicating an increase in plasma volume.

Hemoglobin was estimated by several well-known methods, as those of Tallqvist and Sahli, but the method that gave the most accurate results was carried out by means of a Duboscq colorimeter. One c.c. of the first sample of

* Submitted for publication Feb. 22, 1918.

* From the Laboratories of Physiology, Pharmacology and Physiological Chemistry, University of Pittsburgh School of Medicine.

1. Malcolm, J. D.: Lancet, London, 1905, **2,** 577. British Medical Research Committee, *ibid.*, 1917, **1,** 502. Bainbridge, F. A.: *Ibid.*, 1917, **2,** 51.

2. Guthrie, C. C., and Guthrie, F. V.: Proc. Soc. for Exper. Biol. and Med., 1914, **11,** 148. Guthrie, C. C.: Proc. Am. Phys. Soc. for 1917.

3. Guthrie, C. C.: Jour. Am. Med. Assn., 1917, **69,** 1394

blood taken was added to and thoroughly shaken with 99 c.c. of water. Ten c.c. of this mixture were placed in each of the colorimeter cups and a reading taken to determine if the values on the two sides were the same. One cup was then emptied and refilled with a blood-water mixture prepared from a blood sample taken after shock was induced. It was read against the blood mixture from the sample taken before shock, contained in the other cup. The first sample, or standard, was taken as 100 per cent. and the hemoglobin content of subsequent samples as expressed in terms of per cent. of the standard. The hemoglobin values thus expressed, therefore, are comparative.

Concentration of hemoglobin in the blood progressively decreased, but in no instance was the change of sufficient magnitude to be considered as causally related to shock. The decline in concentration must have been due to entrance of liquid into the blood, as there was no evidence of loss of hemoglobin save that due to blood lost from operation and removed for examination.

Change in the colorimeter value of hemoglobin would influence the results. There is no evidence that material change of this character occurs in shock. To determine the possible influence of acidosis, experiments were made by adding lactic acid to blood and observing the effect on colorimeter readings. Until the reaction of the blood was altered in far greater degree than was observed in shock, in fact, not until the neutrality point had been passed, was there any material change in the colorimeter readings. When change was so induced, it was in the direction of increased value, and was associated with a change in the physical state of the solution as indicated by opalescence which passed to cloudiness.

Samples of blood differing only in oxygenation were diluted with water and tested colorimetrically without appreciable differences in values.

The working errors of all the tests were determined by making readings on a standard blood and a blood prepared by mixing equal parts of the standard blood and clear serum. The error in specific gravity was very slight. By repeated trials it was determined that the error in estimating hemoglobin by the Duboscq colorimeter method was under 2 per cent. The errors by the other methods, in our hands, were greater, in order of accuracy being hematokrit, Sahli's hemoglobin method, red cell count and Tallqvist's hemoglobin method. Of course, familiarity with methods and the personal equation are very large determining factors in the results of such comparative tests, and all we wish to indicate is that we were able in control tests to follow blood changes as determined by specific gravity, relative hemoglobin content, and blood sediment volume with comparatively small errors.

Viscosity was determined by measuring the rate of flow by forcing the liquid through a small bore tube with a constant pressure, and by means of a form of stalagmometer, gravity being the propelling force. Viscosity varies indirectly as the rate of flow, and alterations are expressed in comparative terms. In all instances observed, alterations in viscosity have been of moderate degree and have varied directly with specific gravity, blood sediment and hemoglobin. The magnitude of change in viscosity observed is too small to be of important significance, since enormous alterations in viscosity without profound circulatory impairment have been observed.[4] In shock there has been no evidence of increase in tissue liquids; in fact, rather the tissues have more the appearance of being dry and shrunken. Also, there has been evidence of decrease in urine formation (no escape of urine during the experiment, and the bladder found to be empty at its conclusion), which would tend to result in retention of liquid by the blood.

Freezing Point.—A form of Beckmann's apparatus was used for determining the freezing point of blood. Variations during the course of an experiment occurred, but the end results indicate a somewhat greater depression of the

4. Stewart, G. N.: Manual of Physiology, New York, 1914, p. 23.

freezing point after shock. Differences observed are considered too small to be of significant importance.

Blood volume estimations were made from specific gravity, hematokrit, red cell count and hemoglobin findings. The figures given are relative, and indicate dilution rather than actual blood volume, as they are not corrected for blood removed or lost. An increase in volume indicates an increase of plasma resulting in a decreased concentration of red corpuscles.

TABLE 1.—RESULTS BEFORE AND IN SHOCK

	Before Shock	In Shock	Before Shock	In Shock
	Exp. IV, May 2, 1912		Exp. V, May 10, 1912	
Time	3: 40	5: 05	11: 15	12: 55
Blood pressure	148	27	178	60
Blood specific gravity	1.061	1.057	1.061	1.057
Blood freezing point	—0.634	0.646	—0.619	—0.643
Blood vol. corpuscles*	51.6	45.0	51.6	45.0
Blood volume*	100.0	114.6	100.0	114.6
	Exp. VII, May 23, 1912		Exp. IX, Oct. 31, 1912	
Time	2: 05	3: 30	3: 10	5: 15
Blood pressure	210	11	166	50
Blood specific gravity	1.058	1.054	1.067	1.067
Blood freezing point	—0.587	—0.585	—0.592	—0.617
Blood vol. corpuscles*	46.6	40.0	100.0	100.0
Blood volume*	100.0	116.5	100.0	100.0
	Exp. X, Nov. 4, 1912		Exp. XVII, May 19, 1917	
Time	2: 35	4: 55	2: 47	4: 58
Blood pressure	172	56	194	58
Blood specific gravity	1.065	1.053	1.068	1.062
Blood freezing point	—0.590	—0.620	....	....
Blood sediment volume	....	....	64	56
Blood hemoglobin	....	....	100.0	80.9
Blood red cell count	....	....	10,389,600	7,992,000
Blood viscosity	....	....	100.0	96.3
Blood vol. corpuscles*	58.3	38.3	63.4	53.3
Blood volume*	100.0	152.2	100.0	118.9; 114.2; 123.6
	Exp. XVIII, May 26, 1917		Exp. XX, June 2, 1917	
Time	3: 00	4: 58	2: 38	4: 55
Blood pressure	216	88	168	33
Blood specific gravity	1.064	1.060	....	....
Blood sediment volume	58.5	52.0	....	....
Blood hemoglobin.	100.0	94.0	100.0	92.0
Blood viscosity	100.0	96.0	....	....
Blood vol. corpuscles*	56.6	50.0	....	....
Blood volume*	100.0	113.2; 112.5; 106.3	100.0	107.1

* Calculated.

Blood pressure, mean arterial	Av.	182	48
Specific gravity, determined by weighing	Av.	1.063	1.059
Freezing point, degrees Centigrade	Av.	—0.604	—0.622
Blood sediment volume, per cent. by hematokrit	Av.	61.3	54.0
Hemoglobin, relative per cent. by Duboscq colorimeter	Av.	100.0	89.0
Red cell count, number per cubic millimeter	Av.	....	....
Viscosity, relative per cent	Av.	100.0	96.2
Calculated volume corpuscles, from specific gravity	Av.	54.7	45.3
Blood volume, calculated from specific gravity, sediment volume by hematokrit and hemoglobin	Av.	100.0	117.6

TABLE 2.—SUCCESSIVE BLOOD FINDINGS DURING THE COURSE OF AN EXPERIMENT

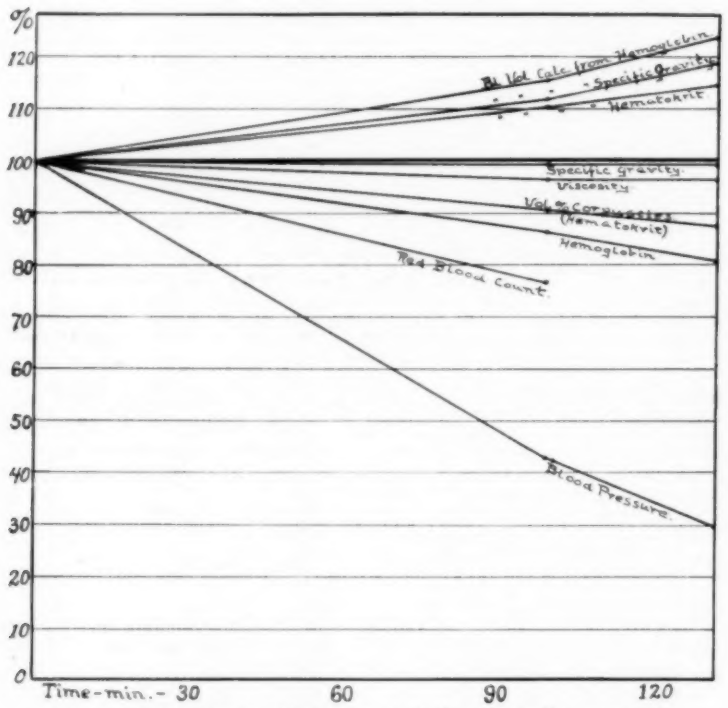
Time	11: 15	11: 45*	12: 25	12: 55
Blood pressure	178	200	109	60
Blood specific gravity	1.061	1.059	1.058	1.057
Blood freezing point	—0.619°	—0.628°	—0.629°	—0.643°

* 11: 26 began strong nerve stimulation.

DISCUSSION

The results show decrease in concentration of the red blood corpuscles. This is interpreted as due to entrance of liquid into the blood.

The degree and time of development of the shock induced varied more than the blood findings. Changes in the blood appear to bear a closer relation to length of experiment and amount of blood withdrawn than to the degree of shock. From this, and from the comparatively



Results of Experiment XVII, May 19, 1917, graphically expressed.

small alterations in the blood, it seems clear that such changes in the blood at most were of minor causative significance in these experiments.

It is known, for example, that following hemorrhage, liquid enters the blood, the concentration of the formed elements (red cells), specific gravity and per cent. of hemoglobin being thereby diminished. In shock associated with hemorrhage, therefore, this tendency would have to be more than counterbalanced for a concentration of the blood to occur. Injury of the capillary endothelium is known to result,

under certain conditions, in the abnormal passage of liquid from the blood into the tissues. Such injury may result from toxic substances introduced into the blood stream, as peptone, or from asphyxiation, as venous obstruction, or temporary arterial obstruction. In shock there is no reason for surmising the presence of a toxic substance capable of such injury to the capillary endothelium, so it would be necessary to surmise an adequate degree of asphyxia.

No doubt the respiratory value of the circulation per unit of tissue is decreased under such conditions, but there is reason for believing that the respiratory demand of many of the tissues also is decreased, the reason being that tissue demand varies directly as activity, and in shock many tissue activities are diminished, as of voluntary muscles and kidneys. The question becomes a quantitative one and sufficiently accurate data for decisively answering it is lacking. As having an interesting relation to the question are observations on the relative susceptibility of different tissues to anemia and certain observations on the relation of preservation of activity of peripheral nervous mechanisms and of vascular endothelium under abnormal conditions. As to the relative susceptibility of vascular endothelium in decline of the respiratory value of the circulation, we have no direct experimental findings. It is generally held, however, that nervous mechanisms (cells and synapses) are the structures first to show impairment and loss of function under such conditions, and in profound shock, activity of even the more highly specialized nervous mechanisms, that is, the least resistant to anemia, as those of consciousness, may not be entirely lost. It would seem improbable, therefore, that at such a stage, much impairment of the capillary endothelium has occurred. It may be that certain capillary areas are more anemic than those of the brain, but in the event of such local impairment the decrease of blood in the areas affected would be against the probability of the escape of much blood liquid. In conformity with this, the superficial tissues appear bloodless and shrunken.

Some years ago experimental observations were made[5] which seem to have a bearing on the question. The posterior trunk and extremities of dogs were removed, posterior to the kidneys, and perfused through the aorta with blood diluted with Locke's solution. The volume of the perfusion mixture was followed and muscular response to nerve stimulation was tested from time to time. There was little change in the blood mixture volume until marked decrease in muscular response occurred, at which time, or soon thereafter, the volume of the blood mixture rapidly decreased and the tissues became markedly edematous. In profound shock peripheral muscular activity and capability to

5. With Prof. Hugh McGuigan.

respond to nerve stimulation is not lost, so from this standpoint, too, it would seem improbable that at such a time the capillary endothelium is seriously damaged.

According to Bayliss,[6] "Filtration is one of the factors in the production of lymph, since the intravascular pressure is greater than that in the tissue spaces; but Starling has insisted on the importance of osmotic pressure in addition. It is, in fact, clear that a rise in the osmotic pressure of the lymph, however this rise is produced, will result in the passage of water from the blood to the lymph and an increase in the volume present." He says that the entrance of liquid into the blood after hemorrhage is due to the higher osmotic pressure of blood than lymph, and that the decrease in blood pressure after hemorrhage permits the entrance of water into the blood from the tissues, normally the combined forces of mechanical and osmotic pressures of the blood balancing or overtopping that of the lymph.

However this may be, and differences of opinion as to the mechanism of lymph formation as well as to the relative osmotic pressures of blood and tissue liquid and lymph exist, the interpretation seems rather more in harmony with the view that in shock, conditions are more favorable for the entrance of liquid into, than passage from, the blood vessels.

The observations on the osmotic pressure of blood before and after shock, as indicated by depression of the freezing point, did not reveal alterations of magnitude considered adequate to warrant a conclusion as to the possible effect on blood volume. No similar observations were made on lymph, and therefore, no comparison of osmotic conditions in blood and lymph are possible in these experiments. But, since tissue activities were less after shock, and since such increased concentration in tissues is due to substances readily permeating the blood stream, and since there was a marked decrease in renal activity, it seems reasonable to conclude from the comparatively slight alterations in the osmotic pressure of the blood, that osmotic pressure of the tissue liquids was not greatly altered. The concentration of the blood following restoration of the circulation in the posterior trunk after temporary anemia (stasis or asphyxiation) induced by vascular occlusion concords with these views. And further support is afforded by the observation that after a period of restored circulation, concentration of the blood ceased and soon again began to diminish. (See Exper. XXI, June 12, 1917.)

The rôle of acidosis in the interchange of liquid between the blood and tissue liquids[7] should be considered, but in the absence of accurate

6. Bayliss, W. M.: Principles of General Physiology, London, 1915, p. 165.
7. Fischer, Martin: Edema and Nephritis, New York, 1915.

data, no conclusions are possible. It would seem, however, to be extremely doubtful that the comparatively slight change in blood reaction observed in certain shocked animals would indicate a degree of tissue acidosis of magnitude sufficient to be of material influence.

In conclusion, we wish to emphasize that these observations were made chiefly in a search for conditions having possible causal relations to the type of shock investigated — not phenomena possibly resulting in late conditions resulting from shock, or conditions possibly occurring in other types of shock. It is not difficult to imagine types of shock in which decrease in total blood volume is a factor of consequential magnitude, as shock associated with hemorrhage, or with extensive tissue traumatization and destruction.

That concentration of the blood may be induced in shock is indicated by the following observation:

Experiment XXI, June 12, 1917. After the arterial blood pressure had been reduced to under 60 mm. Hg., the thoracic aorta was temporarily occluded. Before aortic occlusion the relative per cent. of hemoglobin had decreased. Following release of the aorta, that is, after the circulation was restored in an area temporarily rendered anemic, for a time the relative per cent. of hemoglobin increased.

It is not certain from this one observation that an actual concentration occurred. But it seems probable, for considered serially, before aortic occlusion the percentages were 100, 87.7 and 75.7, and after, 94.3, 101 and 90.0. Since it is well known that circulation through a part previously subjected to profound anemia is associated with edema, this result is to be attributed to the anemia factor induced through aortic occlusion and not due to the condition of shock itself.

In such conditions, associated with marked decrease in blood volume, restoration of blood volume is indicated.[8] But in shock not associated with such conditions the indications for such therapeutic measures are less clearly defined.

CONCLUSIONS

1. In the condition investigated, alterations in blood volume causatively were unimportant.

2. Evidence of entrance of liquid into the blood was obtained.

---

8. Guthrie, C. C.: Blood Vessel Surgery and Its Applications, London, 1912, p. 347.

THE LIGATION OF CORONARY ARTERIES WITH ELECTROCARDIOGRAPHIC STUDY*

FRED M. SMITH M.D.
Assistant in Medicine, Rush Medical College
CHICAGO

This article is based on a study of sixty-six dogs in which known myocardial lesions had been produced by the ligation of definite branches of the coronary arteries of the heart. While the experiments were made with the primary object of determining the change in the electrocardiograms brought about by these ligations, other results, anatomic and pathologic, are deemed worthy of brief mention.

Method.—Dogs were anesthetized with ether and electrocardiograms taken. The chest was surgically prepared and a tracheal cannula introduced for positive pressure. An incision was made parallel to the sternum at about the left costosternal margin, from the third to the sixth rib, then to the left in the fifth interspace. The flap, including the deep muscle layer down to the ribs, was dissected back. Blunt scissors were pushed through the intercostal muscle in the fifth interspace into the pleural cavity, and this incision was carried from the sternum well lateralward. The third to the fifth rib, inclusive, were severed at the costosternal margin and the ribs retracted, thus affording a good exposure of the heart. This exposure was especially satisfactory for the ramus descendens anterior sinister. To ligate the circumflexus sinister to the best advantage the incision had to be carried especially far to the left side with the animal lying on the right side. To expose the right coronary artery an incision similar to the one described was made on the right side of the chest. The pericardium was slit as nearly as possible over the desired artery, which was ligated with strong linen. The pericardial sac and chest cavity were then closed as quickly as possible without regard to the pleura.

Electrocardiograms were taken before the ligations. Early in the work records were made immediately following the ligation and at intervals of ten minutes, over a period of thirty to forty minutes, except in two cases, in which observations were made over a period of four hours. There seemed to be no special advantage in taking these frequent records, so that later they were ordinarily taken at the end of the operation, which was usually from twenty to thirty minutes following the ligation, and then not for several hours.

During the postoperative periods, records were taken at varying intervals. In the first thirty animals the interval was from seven to ten days. Later, electrocardiograms were taken every day for the first week or ten days. After this period every week. Frequent observations in the early postoperative course were found to be desirable.

The dogs were watched for evidence of cardiac failure and were frequently tested for such condition by forced exercise. Signs of other diseases, such as infections, were also noted. In case of death, an early necropsy was performed, especial attention being paid to the lesions found in the heart, their location, extent and histologic structure.

---

* Submitted for publication Feb. 16, 1918.

* This investigation was aided by funds given by Madam C. H. McCormick and R. T. Crane, Jr.

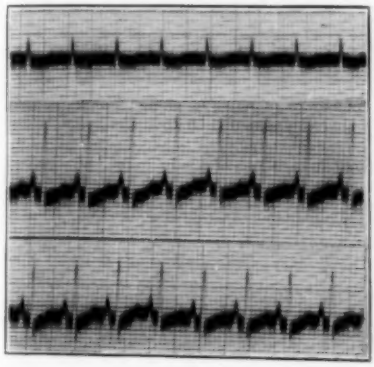


Fig. 1.

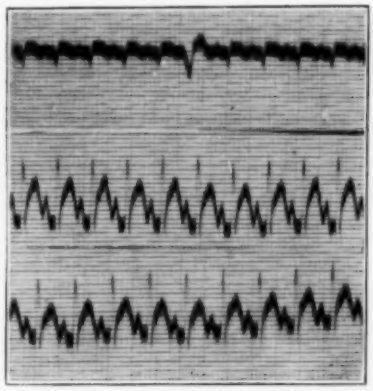


Fig. 2.

Fig. 1.—Normal electrocardiogram of a dog.

Fig. 2.—Dog 48. The record was taken twenty-five minutes following the ligation of the ramus descendens anterior sinister and the first descending branch of the ramus circumflex sinister. The T-wave is markedly elevated—left ventricular extrasystole in Lead I.

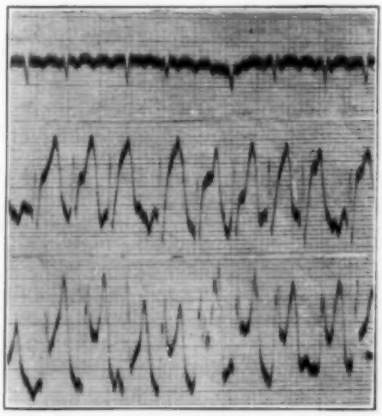


Fig. 3.

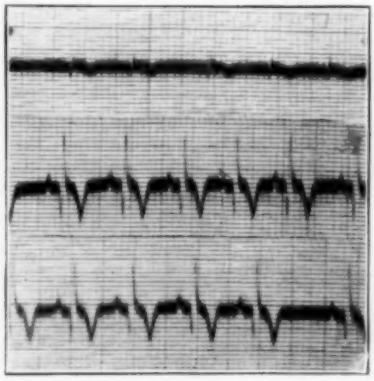


Fig. 4.

Fig. 3.—Dog 17. Record taken five minutes following the ligation of the ramus circumflexus sinister—auricular flutter; auricular rate 500; ventricular rate 166-250. The T-wave is elevated as in Figure 2.

Fig. 4.—Dog 40. The electrocardiogram was taken five days after the ligation of the ramus descendens anterior and the first descending branch of the ramus circumflexus sinister. The T-wave is sharply negative in Leads II and III. It was strongly positive immediately following operation.

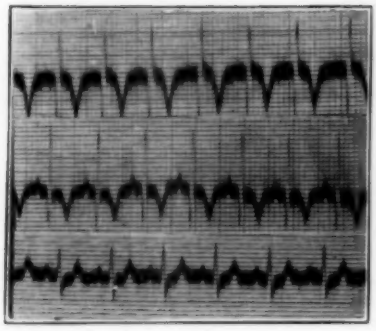


Fig. 5.

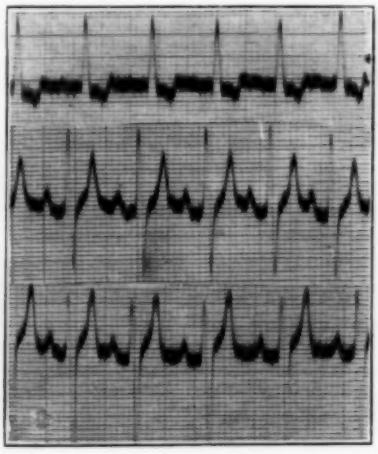


Fig. 6.

Fig. 5.—Dog 54. The electrocardiogram was taken two days after the ligation of the first two lateral branches of the ramus descendens anterior and the first descending branch of the ramus circumflexus sinister. The T-wave in Leads II and III is sharply negative. The T in Lead III has become positive.

Fig. 6.—Dog 29. The record was taken two days after the ligation of the right coronary artery. There is a left ventricular preponderance. The T-wave in Leads II and III has changed from a negative to a markedly positive phase.

Fig. 7.

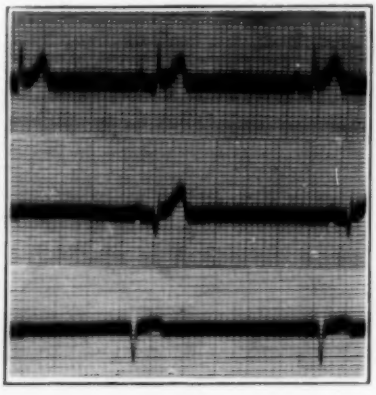


Fig. 8.

Fig. 7.—Dog 8. The record was taken thirty-eight days following the ligation of the ramus descendens anterior sinister. The T-wave is negative in all leads.

Fig. 8.—Dog 20. Electrocardiogram taken fifteen days following operation. An attempt was made to ligate the ramus circumflexus sinister. The ligature was around the vessel at necropsy, but the lumen was only partially occluded. The moderate left ventricular hypertrophy indicated by the electrocardiogram was verified at necropsy.

Fig. 9.

Fig. 10.

Fig. 9.—Dog 16. The record was made fifteen days following the ligation of the ramus circumflex sinister. The T-wave in Leads II and III has grown positive from a sharply negative phase. There are right ventricular premature contractions.

Fig. 10.—Dog 16. Record taken thirty-five days following operation. The R-wave in Leads I and III is blunt. This was the only record of the series which showed this condition. The ramus circumflexus sinister was ligated.

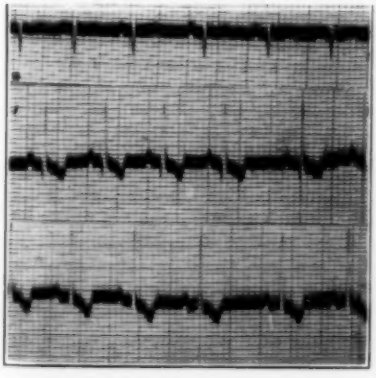


Fig. 11.

Fig. 12.

Fig. 11.—Dog 1. Record taken fifty-one days after ligation of the ramus descendens anterior sinister. The hypertrophy of the right ventricle indicated by the electrocardiogram was verified at necropsy.

Fig. 12.—Dog 18. Record taken twenty-six days following the ligation of the ramus circumflexus sinister. It shows the onset of two attacks of paroxysmal tachycardia.

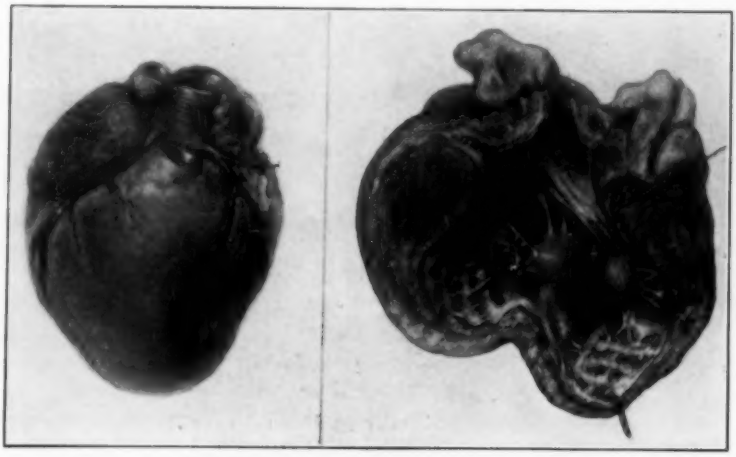


Fig. 13.—The ramus descendens anterior sinister is ligated. The lesion is typical of that resulting from the ligation of this artery. There is a thinning and fibrosis of the anterior wall of the left ventricle and septum especially marked at the apex.

Fig. 14.—The ramus circumflexus sinister is ligated at the site of the ligature. The external change is a slight sinking and thinning of the posterior wall of the left ventricle. The endocardial change is a fibrosis of the posterior papillary muscle and in the immediate vicinity.

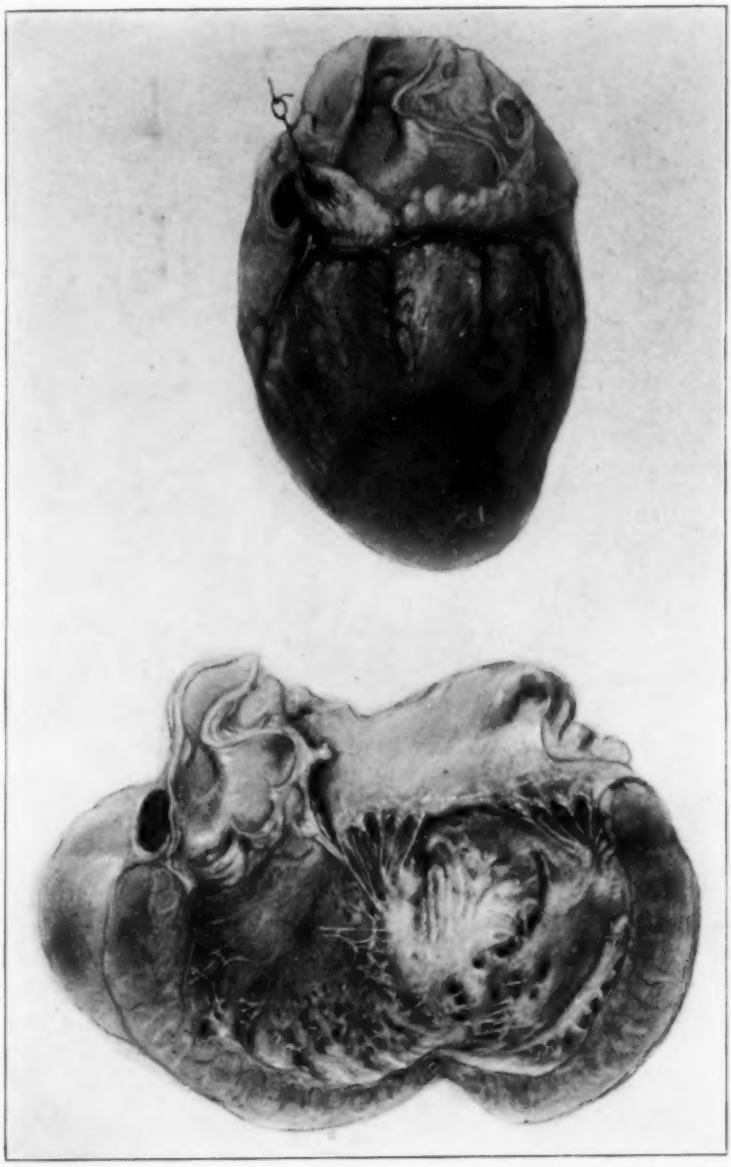


Fig. 15.—The first descending and the large posterior descending branches of the ramus circumflexus sinister were ligated. Illustration shows a fibrosis of the posterior papillary and a slight involvement of the anterior papillary muscle.

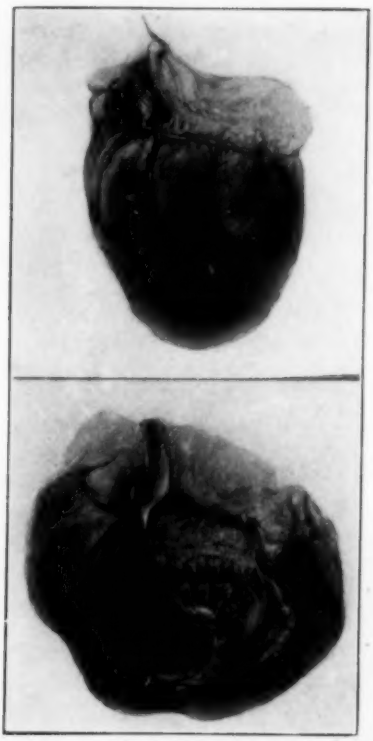


Fig. 16.—The second descending branch and the posterior portion of the ramus circumflexus sinister were ligated. The posterior papillary muscle has changed to a knot of fibrous tissue.

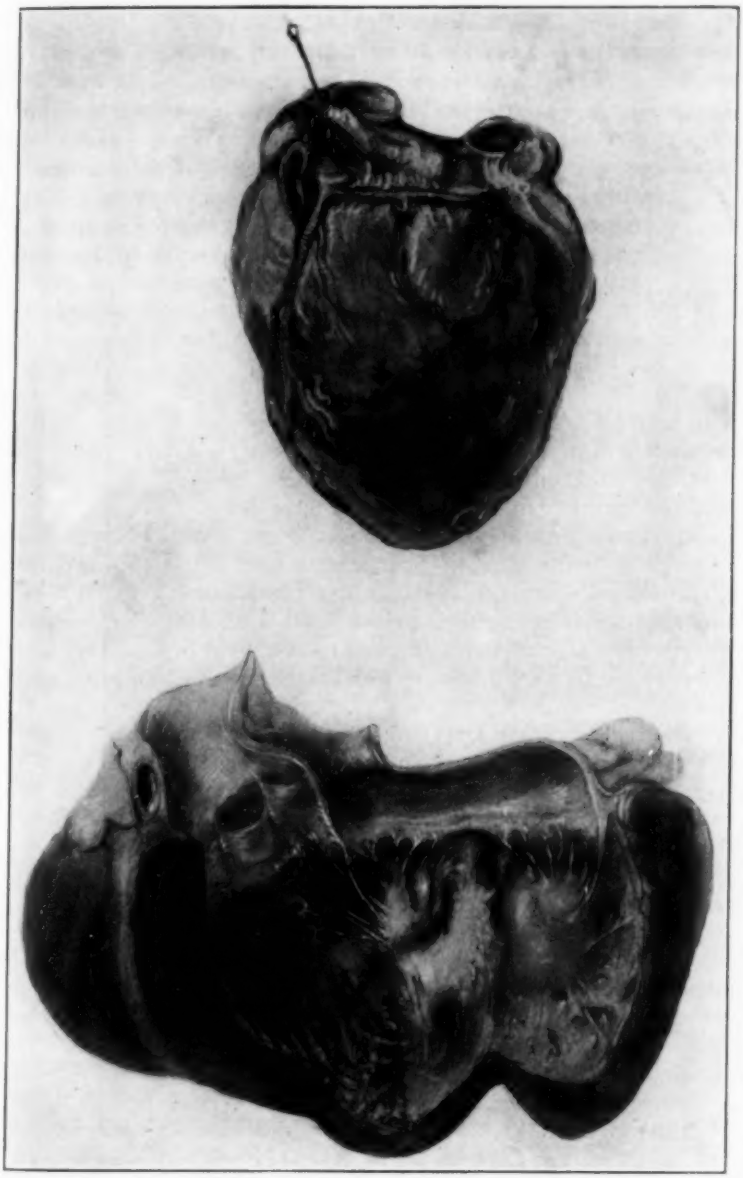


Fig. 17.—The anterior descending branch and the posterior descending portion of the ramus circumflexus sinister were ligated. The resulting endocardial lesion is a fibrosis of the posterior papillary muscle, showing the constancy of the lesion resulting from the ligation of these arteries.

Artery Ligated.—In eleven dogs the ramus descendens anterior sinister was ligated from 1 to 2 cm. from its origin. Dog 2 died within two minutes following the ligation. The ventricles suddenly went into fibrillation. It was afterward discovered that the dog had been previously used by Dr. Woodyatt for sugar injection. It is possible that before our operation there was disturbed function of the heart, as it was noted that the electrocardiogram taken before operation differed from the normal in that the T-wave was distinctly negative in all leads.

Ten dogs survived the operation, one died from sepsis on the eighth day. Dog 9 died on the seventeenth day with symptoms of failing myocardium. At necropsy the left ventricle was dilated and the anterior wall, including the apex, was very thin. The tenth dog of the series was found dead in the cage on the eighteenth day. No cause was found for death. Seven of the series remained in good condition until necropsy. They gained in weight, showed no evidence of fatigue on walking them to and from the electrocardiograph room, which was over one block distant. The time elapsing between operation and necropsy varied from eighteen to sixty-three days.

The ramus circumflexus sinister was ligated from 1 to 2 cm. from its origin in fourteen dogs. Four animals died during the operation; ten awakened from anesthesia in fairly good condition; of these, four died the following night; six animals lived until necropsy time. They became fat and responded well to exercise. In fact, Dog 20 at one time fought several minutes with another dog without being much winded.

The right coronary artery was ligated 2 to 3 cm. from its origin in eight dogs. Four died within five hours. Dog 30 died on the third day from sepsis. Dogs 31 and 32, which gradually grew thin and coughed and vomited frequently, were killed on the tenth and twentieth days, respectively. At necropsy they were found to have bronchopneumonia. Dog 28 was killed on the twenty-eighth day, having completely recovered from the operation.

In eighteen dogs the ramus descendens anterior sinister and one or more branches of the ramus circumflexus sinister were ligated. Nine dogs died within twenty-four hours. Three died from infection in three, twelve and twenty-one days, respectively. Two grew thin and died from failing heart on the fifteenth and seventeenth days. The remaining four dogs were killed by anesthesia in from forty-two to eighty-nine days and necropsy held.

The first lateral branch of the ramus descendens anterior sinister and one or more of the branches of the left circumflex were tied off in sixteen dogs. The portion of the ramus circumflexus sinister was either the large anterior descending or the descending posterior branch. Six dogs died within twelve hours, one from hemorrhage from a sur-

gical blunder. Two became infected and died on the second and tenth days. The remaining eight were in fine condition. There was no evidence of cardiac weakness.

Electrocardiographic Study.—The electrocardiographic curves taken before operation were fairly constant in conformation. Figure 1 represents a type of curve which was encountered in the majority of cases. The R wave in Lead I was always small; it was most prominent in Leads II and III. The T-wave was small in all leads and not infrequently negative. In those dogs in which the T-wave was inverted in all leads, the mortality seemed to be high within twenty-four hours following operation.

Premature Contractions. — Premature contractions were noted usually within a few minutes following the ligation. The type depended on the portion of the heart involved. When the right coronary artery or the circumflex branch of the left, both of which arteries supply blood liberally to the corresponding auricles and ventricles, was ligated, the premature contractions were both auricular and ventricular in type. The ramus descendens anterior sinister supplies portions of the left ventricle and a limited area of the right. Following the ligation of this artery left ventricular premature contractions and an occasional right were often noted.

The number of premature contractions after one hour's time depended in a large degree on the artery ligated. They were usually far more numerous following the occlusion of the right coronary artery and the circumflex branch of the left. It was not uncommon to note many runs of three to five of these premature contractions. This was especially noticeable on the day after operation, when at times there were runs of eight to ten. After this, as a rule, they gradually decreased in number day by day. After one week's time only an occasional one was seen in the electrocardiogram. In some dogs, however — those in which the ramus circumflexus sinister had been ligated —premature contractions were observed in the electrocardiograms until death.

Tachycardia.—In four dogs after the ramus circumflexus sinister had been ligated, premature contractions of the left ventricular type were numerous within one hour's time. There were many small runs of three to four, which gradually increased in number to from six to eight. Finally a permanent tachycardia set in which ended in ventricular fibrillation and death. Possibly this was the explanation of the death of many of the dogs that died within the first twenty-four hours. In fact, one dog, just prior to death, which was twenty-four hours following operation, was observed with such tachycardia. Dog 18 of this series, which had the ramus circumflexus sinister

ligated, had many premature contractions until the time of necropsy. On two occasions the animal was observed in paroxysms of tachycardia. (Fig. 12.) These attacks were usually only a few minutes in duration. They could be produced by exercise and were checked by keeping the dog very quiet.

Ventricular Fibrillation.—Ventricular fibrillation was invariably the outcome of a permanent tachycardia. Fibrillation of the ventricles was not, however, always preceded by tachycardia. In six instances the condition came on quite abruptly soon followed by the death of

TABLE 1.—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF THE RAMUS DESCENDENS ANTERIOR SINISTER

Dog Number	Date of Operation	Vessel Lig.	Date of Necropsy	Duration of Life, Days	Cause of Death
1	1/20/17	Ramus descend. ant. sinister	3/12/17	51	Anesthetized
2	1/23/17	Ramus descend. ant. sinister	1/23/17	Died during operation	Ventricular fibrillation
3	1/24/17	Ramus descend. ant. sinister	3/28/17	63	Anesthetized
4	1/25/17	Ramus descend. ant. sinister	2/17/17	23	Anesthetized
5	1/26/17	Ramus descend. ant. sinister	2/ 3/17	8	Sepsis
6	1/27/17	Ramus descend. ant. sinister	2/17/17	21	Anesthetized
7	1/30/17	Ramus descend. ant. sinister	2/17/17	18	Anesthetized
8	1/31/17	Ramus descend. ant. sinister	3/24/17	52	Anesthetized
9	2/ 1/17	Ramus descend. ant. sinister	2/18/17	17	Anesthetized
10	2/ 3/17	Ramus descend. ant. sinister	2/21/17	18	Failing heart
11	2/ 6/17	Ramus descend. ant. sinister	3/12/17	33	Anesthetized

the animal. In one case the string of the galvanometer fluttered as in ventricular fibrillation; within one minute's time rhythmical contractions followed. No record was taken, for we felt confident that the ventricles were fibrillating and that the experiment would in a few seconds or minutes be finished by the complete stopping of the heart. The dog, however, recovered from the operation and was allowed to live seventy-four days.

In Dog 17 the auricles were fluttering within five minutes following the ligation of the ramus circumflexus sinister. An electrocardiogram taken five minutes later showed auricular fibrillation. This was followed shortly by ventricular fibrillation and death.

T-Wave.—The changes in the T-wave following the ligation of any branch of the left coronary artery were among the most constant and most remarkable, and have not, we believe, been previously recorded by other observers. There was a fairly constant change from the strongly positive peak to a markedly negative, and then a slower return to the positive or iso-electric form. These changes were usually

TABLE 2.—SUMMARY OF RESULTS FOLLOWING THE LIGATION OF THE RAMUS CIRCUMFLEXUS SINISTER

Dog No.	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
12	2/ 7/17	Ramus circumflexus sinister	3/12/17	33	Anesthesized
13	2/ 9/17	Ramus circumflexus sinister	2/17/17	29	Anesthesized
14	2/12/17	Ramus circumflexus sinister	2/12/17	Died during operation	Acute dilatation of heart
15	2/12/17	Ramus circumflexus sinister	2/12/17	Died during operation	Tachycardia; acute dilatation of heart
16	2/14/17	Ramus circumflexus sinister	3/20/17	25	Anesthesized
17	2/15/17	Ramus circumflexus sinister	2/15/17	Died during operation	Ventricular fibrillation; acute dilatation of heart
18	2/17/17	Ramus circumflexus sinister	4/12/17	59	Anesthesized
19	2/21/17	Ramus circumflexus sinister	2/21/17	Died following night	?
20	2/21/17	Ramus circumflexus sinister	2/22/17	54	Anesthesized
21	2/22/17	Ramus circumflexus sinister	2/22/17	Died following night	Acute dilatation of heart
22	3/28/17	Ramus circumflexus sinister	3/28/17	25 minutes following operation	Tachycardia and ventricular fibrillation
23	3/ 3/17	Ramus circumflexus sinister	3/ 3/17	Died following night	Acute dilatation of heart
24	3/ 3/17	Ramus circumflexus sinister	4/14/17	41	Anesthetic
25	3/ 8/17	Ramus circumflexus sinister	3/ 9/17	Morning following	Acute dilatation of heart

as follows: Immediately following the ligation the T-wave became more prominent. As a rule, the height of this wave seemed to vary directly with the size of the branch of the left coronary artery ligated. Where a large vessels was occluded, the T-wave became very tall (Figs. 2 and 3). In some instances it exceeded the height of the R-wave (Fig. 3). On the other hand, when a small artery was ligated the increase in the height of the T-wave was very slight. Within twenty-four hours it became sharply negative (Fig. 4). The larger

the artery the greater was the condition of negativity. This persisted for three or four days, after which it gradually grew less, until by the sixth or seventh day this peak again became positive in one lead, for example, Lead III. The duration of the negative T-wave seemed to depend on the size of the artery ligated. Where the artery was small the negative T lasted not more than from two to four days. While the T-wave usually became positive in Lead III first, followed successively by Lead II and I, occasionally the order was reversed, T in Lead I becoming positive first, followed by II and III.

TABLE 3.—Summary of Results Following Ligation of the Right Coronary Artery

Dog No.	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
26	3/ 6/17	Right coronary artery	3/16/17	Died 6 hours following operation	Tachycardia; acute dilatation of heart
27	3/10/17	Right coronary artery	3/10/17	2 hours following oper.	Tachycardia; acute dilatation of heart
28	3/14/17	Right coronary artery	3/ 4/17	3-4 hours following oper.	Acute dilatation of heart
29	3/11/17	Right coronary artery	4/14/17	28	Anesthesized
30	3/17/17	Right coronary artery	3/20/17	3	Sepsis
31	3/21/17	Right coronary artery	3/31/17	10	Anesthesized; bronchopneumonia
32	3/24/17	Right coronary artery	4/13/17	20	Bronchopneumonia
33	3/27/17	Right coronary artery	3/22/17	Died following night	Acute dilatation of heart

The change of the T-wave from a negative to a positive phase was a gradual one, but progressed until the curve became markedly positive. This condition was usually observed from the second to the fourth week, and was frequently associated with a low voltage R-wave (Fig. 9).

After the fourth week the T-wave again became iso-electric or negative in one or more leads and remained so until necropsy. In some cases this wave was very much below the base line (Fig. 7). This was especially true after the ligation of large arteries, as the ramus descendens anterior and circumflex sinister.

Cardiac Hypertrophy.—Those dogs in which the ramus descendens anterior sinister was ligated, after a period of from four to six weeks, gave an electrocardiogram typical of right ventricular preponderance. At necropsy the right ventricle was found hypertrophied (Fig. 11). Those dogs in which small branches of the left coronary artery were

ligated, developed electrocardiograms typical of left-side preponderance, which was also verified at necropsy.

Pathology.—The pathologic lesions resulting from the ligation of the ramus descendens anterior were fairly constant in type, but varied widely in the extent of the involvement of the heart wall. This would suggest the possibility of a difference in the amount of collateral circulation. Externally there was invariably a triangular area of depression on the anterior surface of the heart along the line of the interventricular septum, involving the left ventricular wall (Fig. 13). The base of this triangle was at the apex of the heart. This area was pale in color and soft or firm in consistency, depending on the age of the lesion. There was, however, often an area occupying the apex that was of soft consistency regardless of the age of the lesion and the amount of fibrosis in the surrounding tissue. In six hearts the ventricular wall at the apex was reduced almost to paper thickness, with beginning aneurism. This was observed in those hearts in which the lesion was extensive.

The endocardial degeneration was more extensive than the epicardial. The endocardium of the lower half of the septum, and the anterior left ventricular wall, including the apex and a small portion of the right ventricle adjoining the septum, were usually involved. Occasionally the base of the anterior papillary muscle was pinched off by the contraction of the fibrous tissue which later developed. The endocardium was pale or mottled in appearance, soft or firm in consistency, depending on the age of the lesion. In a few instances the lower portion of the septum was quite thin. Figure 13 illustrates a typical lesion resulting from the ligation of the ramus descendens anterior sinister.

The pathologic findings resulting from the ligation of the ramus circumflexus sinister were the most surprising, in that the external changes were comparatively small; in fact, in one instance, the only change noted was a small depression in the posterior wall of the left ventricle near the septum (Fig. 14). On palpation, however, the posterior wall of the left ventricle was found to be somewhat thinned out. The endocardial changes were usually confined to the posterior wall of the left ventricle, involving especially the posterior papillary muscle (Fig. 17).

The most extensive endocardial degeneration, as compared with that of the epicardium, was produced by the ligation of the various branches of the ramus circumflexus sinister. The ligation of the first descending branch of this artery generally resulted in fibrosis of the anterior papillary muscle; the ligation of the posterior descending portion of the ramus circumflexus sinister resulted in fibrosis of the posterior papillary muscle. So constant were these results that we could produce lesions of either one of these papillary muscles. In a large percentage of the cases the epicardial change was usually a

TABLE 4.—Summary of Results Following the Ligation of Various Branches of the Ramus Descendens Anterior and Circumflexus Sinister

Dog No.	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
34	4/ 9/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	7/21/17	89	Anesthesia
35	4/11/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/ 4/17	Died 10 minutes after ligation	Acute dilatation of heart
36	4/12/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/12/17	Died following night	Acute dilatation of heart
37	4/14/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/14/17	Died 30 minutes following ligation	Ventricular fibrillation; acute dilatation of heart
38	4/16/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/17/17	Died24hours following operation	Acute dilatation of heart
39	4/18/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	7/ 5/17	78	Failing heart
40	4/21/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	4/21/17	Died 20 minutes following ligation	Ventricular fibrillation; acute dilatation of heart
41	4/23/17	Ramus descendens anterior sinister and first descending branch of circumflexus sinister	8/15/17	83	Anesthesia
42	4/25/17	Lateral branch of ramus descendens anterior and posterior descending portion of circumflexus sinister	4/25/17	Died following night	Acute dilatation of heart
43	4/28/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	6/ 9/17	42	Anesthetized
44	4/30/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/12/17	5	Empyema
45	5/ 2/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/23/17	21	Empyema
46	5/14/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/14/17	Died following night	Acute dilatation of heart
47	5/11/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	5/16/17	Died following night	Acute dilatation of heart
48	5/19/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	7/ 1/17	61	Anesthesia

TABLE 4.—Summary of the Results Following the Ligation of Various Branches of the Ramus Descendens Anterior and Circumflexus Sinister—*Continued*

Dog No.	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
49	5/23/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	5/25/17	2½	Empyema
50	5/26/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	5/30/17	4	Failing heart
51	5/30/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/ 6/17	6	Meningitis
52	6/ 2/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	8/21/17	49	Anesthesia
53	6/ 6/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/14/17	8	Sepsis
54	6/23/17	Lateral branch of ramus descendens anterior and first descending branch of ramus circumflexus sinister	6/23/17	Died 1 hour after operation	Acute dilatation of heart
55	6/25/17	Lateral branch of ramus descendens anterior and posterior portion of ramus circumflexus sinister	7/21/17	26	Anesthesia
56	6/27/17	Lateral branch of ramus descendens anterior and posterior portion of ramus circumflexus sinister	6/27/17	Died following night	Acute dilatation of heart
57	6/30/17	Anterior descending branch and the posterior portion of ramus circumflexus sinister	7/ 6/17	7	Sepsis
58	7/ 7/17	Anterior descending branch and the posterior portion of ramus circumflexus sinister	10/ 6/17	91	Anesthetized
59	7/12/17	Two lateral branches of ramus descendens anterior and descending portion of ramus circumflexus sinister	7/12/17	1 hour following operation	Tachycardia and acute dilatation of the heart
60	7/14/17	Two lateral branches of ramus descendens anterior and descending portion of ramus circumflexus sinister	7/14/17	20 minutes following operation	Hemorrhage from surgical error
61	7/16/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	10/ 6/17	82	Anesthetized

TABLE 4.—Summary of Results Following the Ligation of Various Branches of the Ramus Descendens Anterior and Circumflexus Sinister—(*Continued*)

Dog No.	Date of Operation	Vessel Ligated	Date of Necropsy	Duration of Life, Days	Cause of Death
62	7/18/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	9/30/17	74	Anesthetized
63	7/20/17	Large anterior descending branch and posterior portion of ramus circumflexus sinister	10/ 6/17	77	Anesthetized
64	7/26/17	First lateral branch of ramus descendens anterior sinister and first descending branch of ramus circumflexus sinister	7/28/17	2	Sepsis
65	7/28/17	Two lateral branches of ramus descendens anterior and posterior portion of circumflexus sinister	10/ 6/17	70	Anesthetized
66	7/29/17	Two lateral branches of ramus descendens anterior and posterior portion of circumflexus sinister	7/29/17	Died following night	Acute dilatation of heart

depression less than the size of a five cent piece at the site of the ligation (Figs. 15 and 16).

The lesion resulting from the ligation of the right coronary artery was confined to the lateral and anterior surface of the right ventricle. It was usually about the size of a silver dollar, being more extensive on the endocardial than epicardial side. In addition, there were small areas of fibrosis from 1 to 5 mm. in diameter disseminated throughout the right auricle.

Microscopic Findings.—The microscopic changes were those which have many times been described as resulting from experimental or clinical occlusion. Within twenty-four hours from the time of operation there was an infiltration of round cells and red blood corpuscles within and between the muscle cells. The protoplasm of the cells stained less deeply and the nuclei were paler. After one week fibrous tissue cells had already begun to form, and the muscle cells were in a more advanced stage of degeneration. The fibrous tissue gradually replaced the degenerated cells until by the end of three weeks the fibrosis was fairly extensive.

DISCUSSION

Mortality.—In general the mortality in our series compares closely with that of late experimenters, where ether is used as an anesthetic, where artificial respiration is kept up, and where a rapid aseptic sur-

gical operation is done. The earlier experimenters, as Cohnheim, it will be remembered, had a much higher mortality, and even Porter,[1] whose results were much more favorable because of better technic, lost more dogs than later investigators. The mortality in our series following the ligation of the ramus descendens anterior sinister was 9 per cent. Porter's was 64 per cent. Miller and Matthews[2] had no deaths following the ligation of this artery. Where in addition we ligated one or more small branches of the ramus circumflexus sinister, the mortality was increased to 50 per cent. This was about the same as that from the ligation of either the main trunk of the ramus circumflexus sinister or the right coronary artery, which was 57 per cent. and 54 per cent., respectively. Miller and Matthews had a mortality of only 8.7 per cent. from the ligation of the ramus circumflexus sinister. The difference between our figures and those obtained by Miller and Matthews is, perhaps, explained because we used no digitalis or allied drugs prior or subsequent to ligation. These investigators feel certain that intravenous administration of strophanthin decreased their mortality.

The mortality following the ligation of the first lateral branch of the ramus descendens anterior and either the large anterior or posterior descending branch of the ramus circumflexus sinister was 37½ per cent. These figures approached those obtained from the ligation of the ramus circumflexus sinister or the right coronary artery, yet the area supplied with blood by the last named arteries far exceeds that supplied by the former. Even though the area supplied with blood in the former is less, the papillary muscles are involved, which perhaps may be the explanation for the high death rate.

Pathology.—One fact, strikingly brought out, was that where a lesion was brought about by ligation of the left coronary artery, the softening or fibrosis involved to a much greater extent the endocardial and subendocardial structures than the subpericardial or the body proper of the myocardium. This was true in two cases in man with coronary artery occlusion which we had the opportunity of observing while the work was going on. Oppenheimer and Rothschild[3] have recently called attention to this condition in sclerosis of the coronary arteries. Eight of their cases had occlusion of the ramus descendens anterior of the left coronary artery. While confirming their observa-

1. Porter: Results of Ligation of the Coronary Arteries, Jour. Physiol., 1894, **15,** 121.
2. Miller, J. L., and Matthews, S. A.: Effects on the Heart of Experimental Obstruction of the Left Coronary Artery, THE ARCHIVES INT. MED., 1909, **3,** 476.
3. Oppenheimer and Rothschild: Electrocardiographic Changes Associated with Myocardial Involvement with Special Reference to Prognosis, Jour. Am. Med. Assn., 1917, **69,** 429.

tions as to the location of the pathologic changes, we are not prepared to accept in its entirety their "arborization block" explanation of the electrocardiographic phenomena seen in such cases. We feel that further study of this feature is necessary.

Anastomosis.—The question of an anastomosis between the right and left coronary arteries has been often discussed. Our observations on these dogs lead us to the belief that while the degree of anastomosis is variable, there must often be a fairly free communication between the branches of the right and left arteries or between the smaller branches of the same artery. Otherwise it is difficult to explain the survival of dogs where extensive ligation has been made, the variations in extent of the lesions produced by the obstruction of the same vessel and the comparatively small size of the lesion which frequently results from the occlusion of a large artery.

The same conclusions, we believe, can be drawn with regard to the anastomosis of the coronary arteries in man. In a case that we recently studied, although the ramus descendens anterior sinister and the large anterior descending branch of the circumflexus sinister were completely occluded by thrombi, the only external change was a small depression the size of a fifty cent piece on the anterior wall of the left ventricle. Similar observations have been made by Thorel, Chiari, Merkel, Dock, Herrick[4] and others, in which a fairly rich collateral circulation, capable of functioning, must be assumed to exist as an explanation of the survival of the patient with such a comparatively small area of myocardial involvement after an extensive obstruction of a larger vessel.

Electrocardiograph Study.—The various types of premature contractions, the appearing of these in runs of three to eight, with an occasional onset of tachycardia, have been recorded by Lewis[5] in his work on tachycardia produced by the ligation of the coronary arteries. He observed tachycardia very frequently following the ligation of the right coronary artery, and in one instance following the ligation of the ramus descendens anterior. The majority of these tachycardias described by Lewis did not develop until after one hour subsequent to the ligation. He concluded that even a large number of his dogs would have developed the normal rhythm if he had observed them over a longer period of time. Six out of ten of his animals regained the normal rhythm after developing tachycardia; the remaining four went into ventricular fibrillation and died. In our series, four dogs in which the ramus circumflexus sinister was ligated, developed, within forty minutes, tachycardia which ended in ventricular fibrillation and death.

4. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, Jour. Am. Med. Assn., 1912, **59**, 2015.

5. Lewis: The Experimental Production of Paroxysmal Tachycardia and the Effect of Ligation of the Coronary Arteries, Heart, 1909-1910, **1**, 43.

Dog 18, in which the ramus circumflexus sinister was ligated, was observed on two different occasions in an attack of tachycardia weeks following the operation. The animal was in fine condition at the necropsy which was fifty-nine days from the time of ligation. We have previously stated that the frequency with which paroxysmal tachycardia developed subsequent to the ligation of the ramus circumflexus sinister and the right coronary artery may explain the death of many of these animals the night following the operation. This supposition is made even more plausible by the fact that we observed one animal die in one of these attacks twenty-four hours following operation.

Ventricular fibrillation was observed in six cases. In four instances this abnormal rhythm was preceded by tachycardia and in the remaining two by auricular fibrillation and auricular flutter. Ventricular fibrillation in the dog invariably ended in death. We observed one case in which we believe the normal rhythm was reestablished. Recovery in small animals is very common. Gunn[6] observed this feature in rats. MacWilliams[7] reported recovery in dogs, and recently Robinson and Bredeck[8] have described a case in man in which the normal rhythm returned after a ventricular fibrillation had been well established.

The changes in the T-wave we have already described. If confirmed, these observations may be of considerable value from a diagnostic point of view, at least as concerns the left coronary artery. The early exaggeration of the T-wave, its marked negative drop below the line within twenty-four hours and its more gradual return to its positive position and its final iso-electric or negative location were so characteristic in dogs watched for several days, that similar changes in the wave in man might reasonably be supposed to be due to similar lesions. In fact, one case in man, which will be reported later, was observed in which a clinical diagnosis of coronary thrombosis was made by Dr. James B. Herrick which was verified later at necropsy. The T-wave of the electrocardiogram of the patient ran a course similar to that of the dogs previously described. In other cases believed to be coronary thrombosis similar changes in the electrocardiogram have been seen but no verification of the diagnosis has been made, the patients either living or no necropsy having been obtained.

122 South Michigan Avenue.

It is a great pleasure to acknowledge my indebtedness to Dr. James B. Herrick for his many suggestions and to Dr. E. M. Miller who assisted in the first thirty-three operations.

6. Gunn: Ventricular Fibrillation in Rats' Hearts, Heart, 1913-1914, **5,** 1.
7. MacWilliams: Jour. of Physiol., 1887, **8,** 296.
8. Robinson and Bredeck: Ventricular Fibrillation in Man with Cardiac Recovery, THE ARCHIVES INT. MED., 1917, **20,** 225.

THE CLINICAL REGISTRATION OF CARDIAC MURMURS BY THE DIRECT METHOD*

CARL J. WIGGERS, M.D.
NEW YORK

I. INTRODUCTION

The need of a simple yet efficient device for recording heart sounds, in conjunction with pulse tracings and electrocardiograms, caused Dean and the writer to experiment extensively with various forms of apparatus designed to record heart sounds directly. This experimental work, together with a careful study of published records, convinced us that at the time no so-called "direct method" of sound registration was satisfactory for clinical use. Further experimentation then led us to modify the Frank segment capsule so as to render it more sensitive and protected from extraneous sounds.[1] A mechanical diagram of the apparatus, as improved in minor details, is drawn to scale in Figure 1.

By this apparatus satisfactory records of normal heart sounds can be obtained provided certain simple principles are followed. The clinical adaptability of these capsules could not be guaranteed, however, until their ability to record cardiac murmurs was established. Such a test under hospital conditions was made possible during the months of January and February, 1917, in the wards of the Second Medical Division of Bellevue Hospital through the courtesy and cooperation of Drs. Coleman, Du Bois, Goodridge, Meara, Miller and Niles. For this purpose the capsules were mounted on a table which could be wheeled to the bedside in the wards. To the collection of phonocardiograms thus recorded simultaneously with optical records of the jugular, subclavian or radial pulse were added others from cases kindly diagnosed and referred to the physiological laboratory from the Cornell Medical Dispensary by Dr. Sheldon. The records published in this paper as typical samples of different types of murmurs are offered as evidence that in the majority of cardiac diseases the recognized auscultatory signs can be satisfactorily recorded by this single method.

* Submitted for publication Feb. 7, 1918.

* From the Physiological Laboratory, Cornell University Medical College, and the Second Medical Division, Bellevue Hospital.

1. Wiggers, Carl J., and Dean, Archie, Jr.: Principles and Practice of Registering Heart Sounds by Direct Methods, Am. Jour. Med. Sc., 1917, **153**, 666. Ibid., The Nature and Time Relations of the Fundamental Heart Sounds, Am. Jour. Physiol., 1917, **42**, 476.

II. THE DIFFERENTIATION OF SOUNDS AND MURMURS IN PHONOCARDIOGRAMS

Sounds and murmurs present distinct differences in quality to the ear. In phonocardiograms both are composed of a sequence of vibrations, irregular as regards both their individual amplitudes and periods. It is therefore impossible to differentiate sounds from murmurs on a basis of the regularity, frequency or amplitude of their component vibrations. What, then, are the criteria that differentiate murmurs from sounds in phonocardiograms? Previous investigators have emphasized the importance of establishing the time relations of the vibration groups to other records, such as the pulse or electrocardiogram. This is always most helpful and, when the sounds are very abnormal, often absolutely necessary. Normal sounds have, however, a characteristic grouping of vibrations which, though it varies in dif-

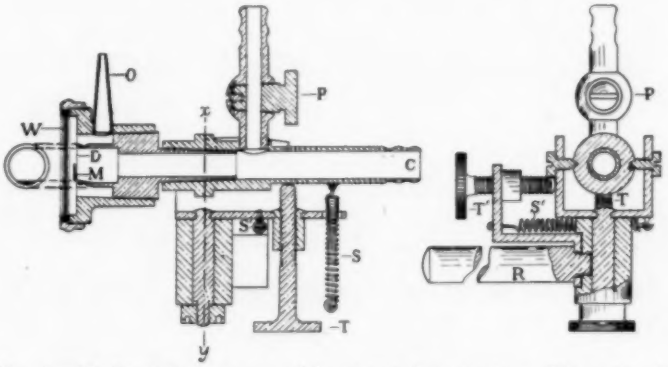


Fig. 1.—Mechanical diagrams of heart-sound apparatus. Figure to right, section through X-Y, scale two thirds actual size; C, tube connecting with stethoscope bell; P, stopcock regulating opening in system; D, rubber film covering segment capsule; M, mirror; O, conical vent communicating with exterior to equalize pressure in chamber; S, S', springs; T, screw for adjusting reflected beam of light horizontally; T', screw for adjusting same laterally; R, rod for clamping apparatus to rigid support; W, glass window for protecting membrane from extraneous vibrations. (Kindly drawn by G. F. Soderstrom.)

ferent individuals, the eye soon learns to distinguish as a sound complex. The characteristics of sounds are far more difficult to describe than to visualize. Two phonocardiograms showing such normal sounds are shown in Figure 2. In B the second sound was somewhat accentuated and, therefore, relative to the first sound, of larger amplitude. The first sound (I) is of longer duration than the second (II). Both sounds reach a maximum amplitude rapidly and, after a swift decrescendo, stop abruptly. If there is any single characteristic that most unfailingly differentiates sounds from murmurs in phonocardiograms

it is the short duration and abrupt cessation of the "sound vibrations" as contrasted with the more prolonged nature of the murmurs. This is in entire accord with our conception of the causes of sounds and murmurs. Neither are sounds in a physical sense but belong to the category of "noises." The so-called "heart sounds" owe their peculiar auditory quality to the fact that vibrations of irregular sequence and amplitude are suddenly produced by the action of a temporary force, hence the damped vibrations soon cease. Murmurs, on the other hand, owe their auditory quality to the fact that vibrations of an irregular nature are produced by a continued force, usually though not always of less intensity than that responsible for sound vibrations.

In order to analyze phonocardiograms it is essential first to recognize the "sound complexes" and then to refer the remaining vibrations

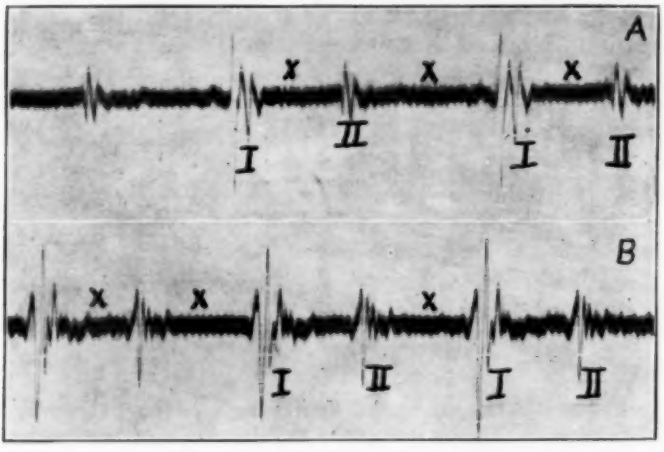


Fig. 2.—Phonocardiogram showing normal heart sounds. In B the second sound is accentuated.

to murmurs. In doing this it is necessary, however, to discount certain unavoidable, accidental vibrations, much as in microscopic diagnosis we disregard artefacts of fixing and staining, or as in auscultation the ear is trained to disregard adventitious sounds. In the phonocardiograms of Figure 2 there may be observed between the sounds small vibrations (X) due to such extracardiac vibrations. These are sometimes somewhat larger and must not be confused with murmurs. In cases in which marked dyspnea is present or other pulmonary sounds are pronounced, they may occasionally obscure murmurs entirely. This is also the case when the murmurs are very soft and the accidental vibrations no greater than normal.

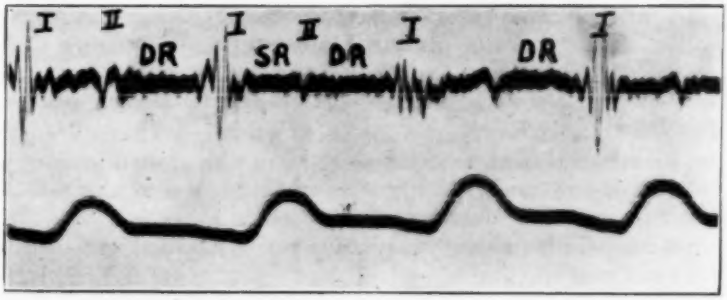


Fig. 3.—Phonocardiogram showing, in addition to heart sounds, systolic friction rub (SR) and diastolic friction rub (DR). Lower record, radial pulse.

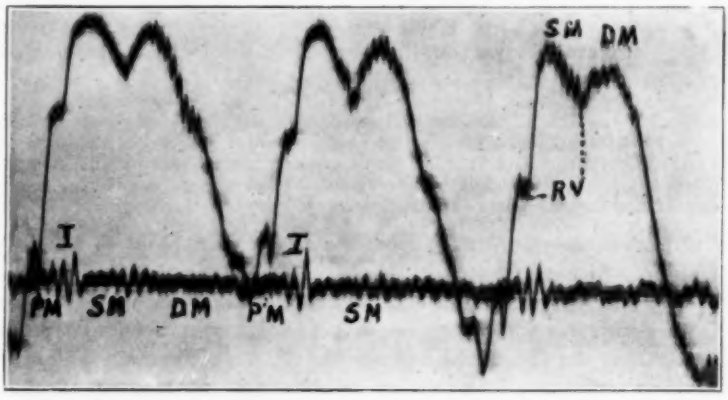


Fig. 4.—Phonocardiogram and jugular tracings from case of aortic insufficiency. Phonocardiogram shows, in addition to first sound (I), presystolic (PM), systolic (SM), and diastolic (DM) murmurs. Systolic and diastolic murmurs are also shown superimposed on the regurgitant wave (RV) of the jugular tracing.

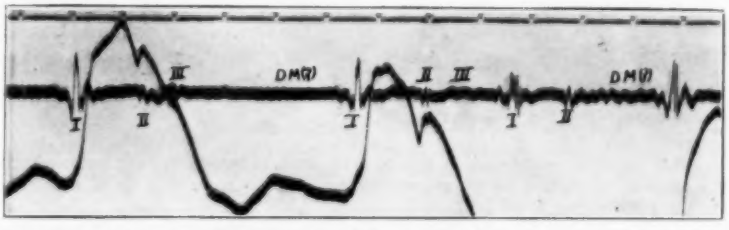


Fig. 5.—Phonocardiogram and subclavian pulse from case of auricular fibrillation. Phonocardiogram shows in addition to heart sounds, a diastolic murmur. Systolic murmur heard on auscultation was not recorded.

III. DESCRIPTION OF PHONOCARDIOGRAMS IN DIFFERENT CARDIAC LESIONS *

CASE J-2.—Mr. W. D. *Acute Pericarditis.* Systolic and diastolic friction rub best heard over the right border of the sternum but distinctly audible at the apex (Dr. Coleman).

From the areas where sounds were heard with greatest intensity by the ear, no satisfactory records either of the heart sounds or the friction rub could be obtained. Over the apex, as shown in Figure 3, the first sound (I) is apparently normal, varying in amplitude with inspiration and expiration as is normal. The second sound (II) is barely indicated. The periods of systole (I to II) and diastole (II to I) are filled with a regular series of vibrations of high frequency (SR, DR), quite different from the accidental vibrations usually present. They are present very clearly during all the periods of diastole, but are only occasionally present as distinct vibrations during systole. The second cycle of Figure 3 shows both the systole (SR) and diastole friction rub (DR) clearly.

CASE J-3.—Mrs. E. G. *Aortic Insufficiency.* Rough diastolic murmur over aortic area transmitted across the sternum, loudest at the level of the third rib. Presystolic (Flint) and systolic murmurs over apex. Systolic and diastolic murmur audible in supraclavicular region. Radial pulse gives tactile impression of a collapsing pulse (Dr. Miller).

Phonocardiograms taken from the apex region (Fig. 4) show the vibrations of the first sound (I) clearly. They are abnormal in character. The second sound is entirely absent. Preceding the first sound there occurs regularly a group of presystolic vibrations (P) corresponding to the presystolic murmur heard on auscultation. Following the first sound and filling the period of systole are a group of vibrations (S) which probably correspond to the systolic murmur but could not be so interpreted without auscultatory aid and the fact that the venous pulse contains "regurgitant waves" (RV) (Niles and Wiggers[2]) with systolic vibrations (SM) superimposed. The second sound is replaced by a series of vibrations which extend into diastole (DM) and correspond to the diastolic murmur heard best further to the right. They are also superimposed on the V wave of the venous tracing (DM).

CASE J-4.—Mr. E. D. *Auricular fibrillation. Mitral lesion.* Systolic murmur at the apex (Drs. Du Bois and Barr).

---

* All records reproduced in this article were reduced in size; consequently the smaller vibrations in some records will appear more clearly if examined with a magnifying hand lens.

2. Niles, Walter L., and Wiggers, Carl J.: The Details of the Photographically Recorded Venous Pulse in Auricular Fibrillation; and the Significance of the Diastolic Waves of the Venous Pulse in Auricular Fibrillation, Jour. Exper. Med., 1917, **25**, 1.

Phonocardiograms taken from the apex (Fig. 5) show vibrations typical of a first and second sound (I, II) and, in the long cycles, a third sound (III) although the latter was not heard on auscultation. The character of the first sound varies from one cycle to another, which is typical in auricular fibrillation or any other form of irregular-

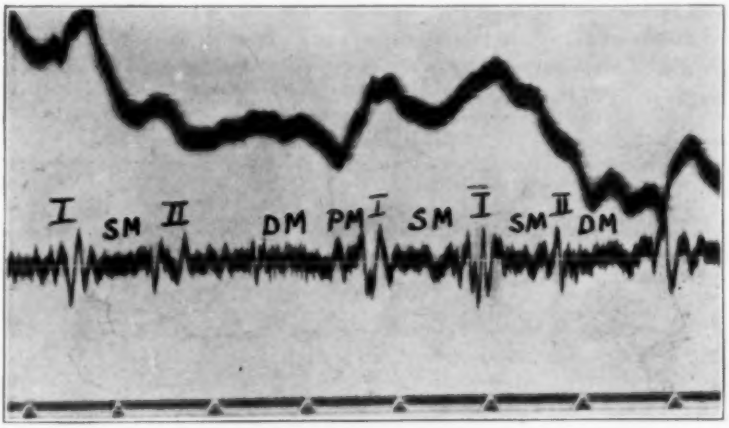


Fig. 6.—Phonocardiogram taken from same patient as Figure 6, showing, in addition to first and second sounds, a presystolic (PM), systolic (SM), and diastolic (DM) murmur. Upper tracing, jugular pulse.

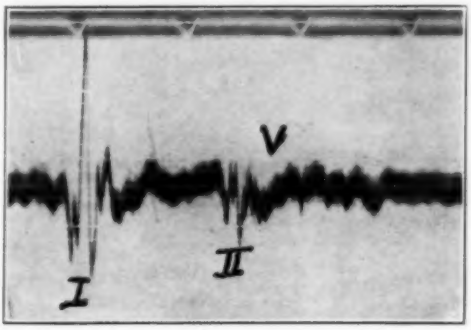


Fig. 7.—Phonocardiogram recorded from case of mitral stenosis. Note peculiar character of first sound and series of vibrations (V) following second sound, indicating a diastolic murmur which could not be heard on auscultation.

ity of the ventricle. Aside from these sounds, vibrations which may be doubtfully referred to as a diastolic murmur are present (DM?). No vibrations due to a systolic murmur distinctly heard on ausculta-

tion are present in this record. By moving the receiving cup slightly to the right a phonocardiogram was obtained (Fig. 6) that showed a distinct systolic murmur. Its character and constancy varied from beat to beat, sometimes following a distinct first sound, as shown in Figure 6; occasionally practically replacing the first sound, as shown in unpublished records. A diastolic murmur is indubitably present in this record, although no note of such a murmur was made at the time of auscultation. The vibrations, in some cycles at least, fill the entire period of diastole right up to the next first sound, so that a presystolic murmur (PM) can be said to exist.

Case J-5.—Mr. J. K. *Mitral stenosis.* Presystolic murmur having a peculiar metallic quality and terminating in a sharp first sound. Systolic shock at the apex, but no thrill (Dr. Niles).

The phonocardiograms recorded (Fig. 7) show a very pronounced series of vibrations quite different from that recorded normally for the

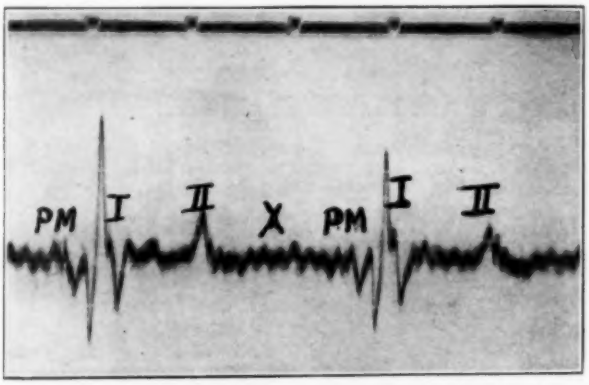


Fig. 8.—Phonocardiogram from case of mitral stenosis, showing, in addition to first and second sounds, a presystolic murmur (PM).

first sound (I). The large wave is evidently indicative of the shock felt on palpation and the sharp quality heard on auscultation. No evidence of the presystolic murmur is indicated. Unfortunately, no other record was obtained, owing to the fact that the patient left the hospital.

The second sound is peculiar in character and followed by a series of vibrations (V) that might indicate a short diastolic murmur. Careful reauscultation failed to elicit such a murmur, however (Dr. Niles).

Case J-6.—Mrs. E. M. *Mitral stenosis.* Loud presystolic murmur over the apex (Dr. Niles).

Many phonocardiograms were taken but all showed nothing except an increased amplitude of the first sound and the peculiar characteristics apparently associated with mitral stenosis. Finally a record was obtained (Fig. 8) that gave clear indication of such a presystolic murmur (PM) running into the vibration composing the first sound.

Case J-7.—Mr. A. F. *Mitral lesions.* Diffuse apex pulsation; rough presystolic murmur at the apex and over the pulmonary area (Dr. Niles).

Phonocardiograms taken from the apex area (Fig. 9) show a series of presystolic variations (PM) separated by a short interval from the first sound (I). The vibrations composing this sound are of approxi-

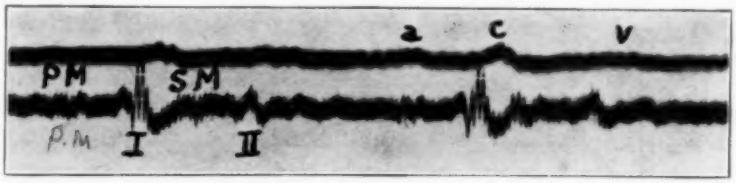


Fig. 9.—Phonocardiogram and jugular pulse found in case with mitral lesions, showing, in addition to first and second sounds, a presystolic murmur (PM) separated from the first sound and a systolic murmur (SM) continuing throughout systole.

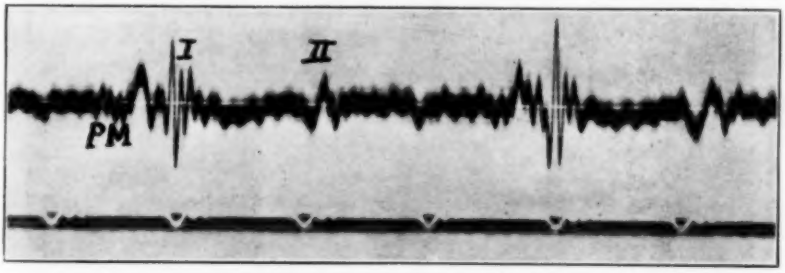


Fig. 10.—Phonocardiogram from a case of mitral stenosis, showing presystolic murmur (PM) merging with the first sound.

mately the same period and are immediately followed by variations responsible for the systolic murmur (SM). The second sound (II) is barely indicated and the period of diastole is free from murmur vibrations.

Case J-8.—Mr. J. B. *Mitral stenosis.* Loud, long presystolic murmur ending in a sharp first sound heard best at the apex (Dr. Du Bois).

Phonocardiograms taken from the apex region (Fig. 10) showed repeatedly a clearly defined set of presystolic vibrations (PM) ending abruptly in the vibration of the first sound (I).

CASE J-9.—Mrs. G. N. *Decompensation of heart. Possible aortic insufficiency or aortic dilatation.* Systolic murmur at the apex. Musical diastolic murmur at the left second intercostal space and over the sternum (Drs. Niles and Miller).

From the area over the aortic region and over the sternum phonocardiograms, such as shown in Figure 11, were recorded. The character of the first sound (I) differs appreciably from normal and varies

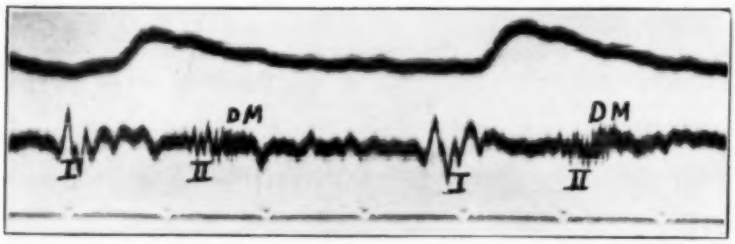


Fig. 11.—Phonocardiogram and radial pulse from a case of cardiac decompensation. Probably aortic insufficiency. Phonocardiogram shows a short, musical diastolic murmur following the second sound.

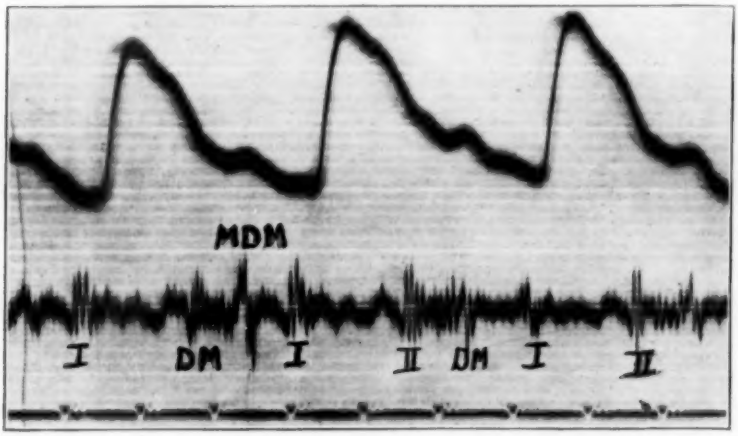


Fig. 12.—Radial pulse and phonocardiogram of case with mitral lesions, showing peculiar first and second sound vibrations and a pronounced diastolic murmur (DM) which sometimes increased in intensity during mid-diastole, as shown at MDM. Details in text.

with the phases of respiration. The second sound is often indicated (II) but is followed immediately by a diastolic series of vibrations having a high frequency and of approximately the same period in successive vibrations, which is typical of musical murmurs. It is loudest early in diastole and becomes diminuendo.

CASE J-10.—Mr. Z. Z. Soft blowing systolic murmur at the apex, sixth intercostal space, 14 cm. from the midsternal line. Presystolic crescendo murmur in the left fourth intercostal space. Soft systolic murmur and loud diastolic murmur over the left second intercostal space, transmitted across the sternum. First sound of poor quality, pulse quite large, Corrigan type (Dr. Meara).

Phonocardiograms recorded from the apex (Fig. 12) show a series of miscellaneous vibrations from which the first sound could not be detected without the guidance of the radial pulse curve. With its aid they were marked (I). They consisted of a few vibrations quite unlike those found in normal hearts and corroborate the auscultatory findings of a sound with poor quality. No clear evidence of the soft systolic blow exists. The second sound (II) in some cycles contains vibrations of larger amplitude than the first sound and is followed by a distinct, irregular series of vibrations (DM) responsible for the diastolic murmur. In others, it is entirely replaced by the diastolic murmur. It is curious how readily diastolic murmurs are registered

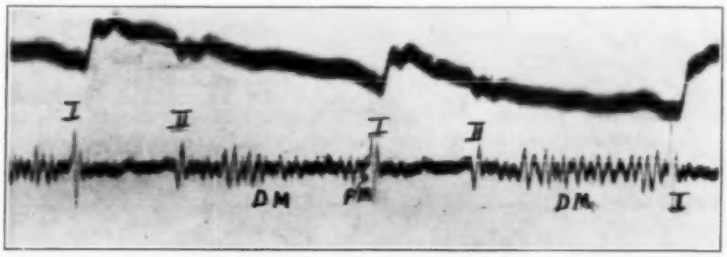


Fig. 13.—Radial pulse and phonocardiogram from a case with mitral lesions. Phonocardiogram shows, in addition to first and second sound, presystolic (PM) and diastolic murmurs (DM), varying from cycle to cycle.

from the apex in cases even when they are not audible in this locality but distinctly present over the more basal portions of the heart. Frequently the diastolic murmur develops a series of larger vibrations in mid-diastole (MDM) which possibly corresponds to the murmur referred to as presystolic in the auscultation notes and heard somewhat higher on the left side. Incidentally, attention may be directed to the fact that the descending limb of the radial pulse, which to the finger gives the sensation of a collapsing pulse, falls rather slowly. The dicrotic notch, however, is low and late in diastole.

CASE J-12.—Mrs. A. R. *Mitral lesions.* Apex beat sixth intercostal space, presystolic murmur ending in accentuated first sound at the apex. Diastolic murmur over the second intercostal space and the sternum (Dr. Sheldon, Cornell Medical Dispensary); also heard over the apex.

Phonocardiograms taken from the apex are shown in Figure 13. The first sound (I) is indicated by a few large vibrations. It is imme-

diately preceded by a series of small vibrations (PM) running into the larger vibrations of the first sound. These probably represent the presystolic murmur heard on auscultation. The systolic period is free from vibrations. The second sound (II) is composed of two large vibrations and is followed after a short interval by a series of coarse waves of relatively large amplitude and irregular periods (DM). They continue throughout diastole and sometimes merge into the presystolic vibrations or the first sound. They correspond to the diastolic murmur.

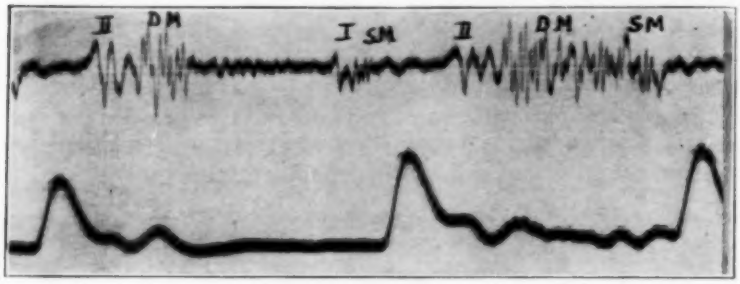


Fig. 14.—Phonocardiogram and radial pulse taken from a case with mitral lesions, showing, in addition to abnormal first and second sounds, a short systolic murmur (SM) and diastolic murmur (DM), varying from cycle to cycle both as to character and duration.

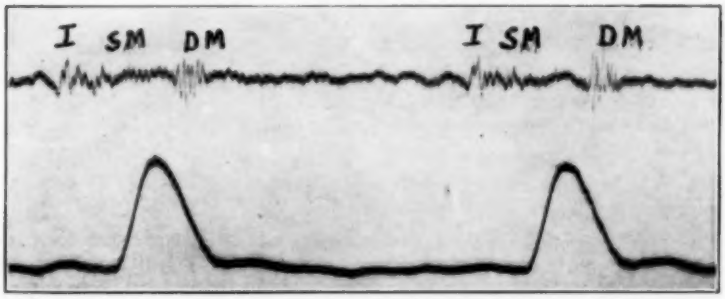


Fig. 15.—Phonocardiogram and radial pulse from a case of mitral regurgitation, showing systolic (SM) and diastolic (DM) murmurs, together with a collapsing pulse in the radial artery.

Case J-13.—Mr. S. C. *Probable mitral lesion.* At the apex are heard a soft systolic murmur and a diastolic rumble varying in duration, quality and intensity. At times a presystolic murmur accompanied by a thrill was present (Dr. Niles).

The apex phonocardiogram (Fig. 14) shows the first sound (I) either entirely supplanted by or continued into a murmur (SM) extending through the early part of systole. The second sound (II)

is followed after a short interval by a murmur (DM) composed of coarse, irregular vibrations. In some beats they extend throughout diastole; in others, occur only in the early part of diastole. No evidence of a presystolic murmur is present in any record. The descending limb of the radial pulse shows a rapid fall, corresponding to the collapsing character felt on palpation.

CASE J-15—Mr. O. E. *Aortic insufficiency.* Systolic murmur at the apex. Diastolic murmur over the aortic area and across the sternum. Collapsing pulse (Dr. Miller).

Phonocardiograms taken over the sternum (Fig. 15) show a first sound (I) of abnormal character followed by a series of systolic vibraitons (SM) representing the murmur heard best over the apex in auscultation. These vibrations continue throughout systole. The second sound is replaced entirely by a series of vibrations (DM) which constitute the early diastolic murmur. The descending limb of the radial pulse falls rapidly, confirming the tactile impression of a collapsing pulse.

IV. SUMMARY OF TYPES OF CARDIAC MURMURS IN PHONOCARDIOGRAMS

Having analyzed the phonocardiograms individually, it remains in conclusion to group the various types of murmurs exemplified in a more orderly array and correlate them with the auscultatory phenomena.

Presystolic Murmurs.—A presystolic murmur may accompany a variety of cardiac conditions. It is most clearly recognized in cases of mitral stenosis in which the auricle continues to contract regularly and efficiently. In such cases the murmurs increase in intensity and end in a characteristic snapping first sound from which alone the diagnosis may sometimes be made. The vibrations responsible for this murmur may be felt as a thrill on palpation and end in a characteristic systolic shock. Such murmurs are illustrated in Figures 8 and 10. When the auricles are fibrillating the presystolic murmur does not always disappear, but the presystolic period may be filled with vibrations continued from the diastolic murmur. This is shown in Figures 6 and 13. Presystolic murmurs may be present in double mitral lesions in which insufficiency predominates. In such cases the murmur does not necessarily end in the typical sharp first sound, but is separated from it by a short interval, as shown in Figure 9. Finally, presystolic murmurs frequently accompany aortic insufficiency. They may be separated from the diastolic murmur by an interval, but not necessarily, as shown in Figure 4.

Systolic Murmurs.—Systolic murmurs of soft, blowing character most frequently accompany mitral insufficiency. They rarely replace the first sound entirely, although the character of this sound may be altered, as shown in Figures 6, 9 and 14. Systolic murmurs are also commonly associated with the diastolic murmurs in aortic insufficiency. Such cases are shown in Figures 4 and 15. Associated mitral or tricuspid lesions or aortic stenosis are, no doubt, sometimes responsible for this systolic murmur. It is possible, also, that the disturbed dynamic pressure relations between the ventricles and aorta in a pure insufficiency may in itself be sufficient to account for the systolic murmur.

Diastolic Murmurs.—Diastolic murmurs may be described as early diastolic, middiastolic and late diastolic. The diastolic murmurs of aortic insufficiency usually occupy the early phase of diastole and may entirely replace the second sound (Fig. 15). They may, however, in undoubted cases extend well into the diastolic period, as shown in Figures 3 and 4. Musical diastolic murmurs follow the second sound and are early diastolic in time, as shown in Figure 11. In no case was such a murmur found to extend into the late diastolic period.

Diastolic murmurs frequently occur in mitral lesions when the auricles are fibrillating. The murmur then varies from cycle to cycle and may fill the entire period of diastole, as shown in Figure 6. They may occur also in mitral stenosis while the auricle is regularly contracting but the rhythm of the heart is slow. This is exemplified in the records of Figure 13 where it is followed in certain beats, by a presystolic murmur. In complex mitral lesions systolic and diastolic murmurs may be so prolonged that they merge, thereby obliterating the intervening first sound as an entity (Fig. 14).

THE PREVENTION OF SIMPLE GOITER IN MAN*

SECOND PAPER

O. P. KIMBALL, M.D., AND DAVID MARINE, M.D.
CLEVELAND

In Article I[1] we gave a brief review of the experimental work on which the assertion is based that simple goiter is probably the easiest of all known diseases to prevent. We gave a survey of the incidence and types of thyroid enlargement in the schoolgirls of Akron (Ohio) from the fifth to the twelfth grades, inclusive, and the plan of prevention used.

The plan in operation was arranged from the standpoint of simplicity, practicability, economy and the possible scientific value of the data obtained. First, a census of the condition of the thyroid gland was taken of all girls between the fifth and twelfth grades, inclusive, and the findings recorded on individual cards. This card will be used throughout the whole series of observations, the condition of the thyroid noted each year and a record of all treatment kept on the back of the card.

No.	Date .....
Name	School .....
Age ..... Weight	Physical Development .....
Grade	Class Standing .....
Tonsils-Adenoids	.....
Thyroid	1 .....
Simple	2 .....
Adenomas	3 .....
Thyroid-tract	4 .....
Duration	.....
Remarks	.....

It was planned that the thyroid examinations should be made by a single examiner in order to make the standard used constant, and the data obtained uniform. At the time of the first examination, however, it was clearly foreseen that Dr. Marine would be called to military duty. Therefore, in order that the junior author should be trained to examine and classify the cases in the November examination as nearly as possible precisely in the same way as was done in the April examination, the April examination was made by both authors conjointly. It is obvious that much of the value of observations of this kind must depend on the uniformity of the methods and classification.

---

* Submitted for publication March 2, 1918.

* From The H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University.

1. The Prevention of Simple Goiter in Man, Jour. Lab. and Clin. Med., 1917, **3**, 40.

The thyroid glands were examined from the standpoint of Normals, Slight, Moderate and Marked Enlargements, Adenomas, Persistent Thyroglossal Tracts, and the girls for gross manifestations of myxedema, or exophthalmic goiter. No obvious case of either myxedema or exophthalmic goiter has been found.

Under *Normal* we have included all glands (*a*) which are not visible as a bulging of the skin across the trachea; (*b*) having a barely detectable band of thyroid tissue across the trachea on palpation, and (*c*) absence of a well defined thyroglossal stalk (so-called pyramidal process).

The cases with *Enlarged Thyroids* have been divided into three arbitrary groups: (1) Slight, (2) Moderate and (3) Marked Enlargement. Under *Slight Enlargement* we have grouped those cases with (*a*) visible bulging of the skin over the thyroid isthmus (except in very stout children), and (*b*) a widened and thickened isthmial band or mass on palpation. If the isthmus can not be seen or felt, it can be felt by having the child swallow while the finger or thumb is held against the trachea just below the cricoid cartilage. Under *Moderate Enlargement* we have grouped those with gross deformity, bulging of the neck laterally from the enlarged lobes and marked bulging of the skin anteriorly from the enlarged isthmus. Under *Marked Enlargement* we have grouped those cases with excessive deformity.

Analysis of Thyroid Examinations.—In April, 1917, 3,872 girls of the fifth to twelfth grades, inclusive, were examined and the general results are given in Table 1. In November, 4,415 girls of the fifth to twelfth grades, inclusive, were examined and the new records are given in Table 1. The new records each year will be classed in this table.

TABLE 1.—CONDITION OF THYROID GLAND

	Normal		Slight Enlargements		Moderate Enlargements		Marked Enlargements		Adenomas	
	Pupils	%	Pupils	%	Pupils	%	Pupils	%	Pupils	%
April, 1917	1,688	43.59	1,931	49.88	246	6.35	7	0.18	29	1.01
Nov., 1917*	831	47.00	820	46.20	121†	6.80				

* Fifth grade girls and girls who entered the Akron schools since April, 1917.

† This number is greater than it would be if only fifth grade pupils were examined; two large schools, one a high school, accidently destroyed all records of those girls not taking treatment, and therefore had to be recorded as new records.

For the prophylactic treatment we selected sodium iodid on the grounds of economy and ease of administration. Regarding the amounts that should be given, we had no data except from animal experimentation, and as we have pointed out repeatedly, exceedingly small amounts of iodin are effective. In all our dispensary work with children we have used either syrup of hydriodic acid or syrup of ferrous iodid, in 1 c.c. doses daily for two or three weeks, repeated twice yearly. The dosage is much less than the therapeutic dose of

iodids in other instances in which they are so extensively used, and there can be no reasonable doubt that the action is very different.

We, therefore, arbitrarily selected to use 2 gm. sodium iodid, given in 0.2 gm. doses each school day, for each pupil in the fifth, sixth, seventh and eighth grades; and 4 gm. in 0.4 gm. doses each school day for each pupil in the ninth, tenth, eleventh and twelfth grades. These amounts were given in May, 1917, but in November, 1917, we gave 2 gm. to each pupil from the fifth to twelfth grades, inclusive, since this amount in the year's use gave such definite results. As was pointed out in the previous paper, it was thought likely that the dose would be materially reduced. This amount (2 gm.) will be given again in April, 1918. The treatment is given at the school by the teacher or principal and the number of doses recorded. A record is kept, both of those who take the treatment and of those who do not, and all pupils are to be examined annually and the thyroid conditions recorded.

A complete reexamination of all girls from the fifth to twelfth grades was made in November, 1917. There were 1,772 new records (Table 1). These include (*a*) this year's *fifth* grade; (*b*) pupils of all grades above the fifth entering Akron schools since April, 1917, and (*c*) all the girls in two schools (*not* taking treatment) whose records had been accidentally destroyed (see footnote, Table 1). All those previously examined were classed either as taking prophylactic treatment or not taking prophylactic treatment. The results are summarized in Table 2.

TABLE 2.—SUMMARY

	Pupils Taking Prophylactic Treatment		Pupils Not Taking Prophylactic Treatment	
	Pupils	%	Pupils	%
Thyroids remained normal	283	100.00	637	74.0
Increased from normal to slight goiter	0	0.0	259	26.0
Small goiters (unaltered)	287	66.0	759	87.0
Small goiters (disappeared)	141	33.5	10	1.2
Small goiters (increased)	2	0.5	103	11.8
Large goiters (unaltered)	34	66.7	106	95.5
Large goiters (decreased)	17	33.3	5	4.5
Total	764		1,879	
Total number of girls examined	4,415			

It will be seen that not a single pupil in whom the thyroid was normal last year and who took iodin, showed any enlargement, while of those not taking iodin, 26 per cent. showed definitely enlarged thyroids — some moderately large goiters. Even more than a prophylactic action is shown in the results — just one third of the goiters marked "small goiters" disappeared; and one third of those marked "moderate goiters" showed a decrease of 2 cm. or more. Accordingly, a distinct therapeutic effect is clearly demonstrated.

It was suggested by some physicians that we would have many cases of iodid rash. We spoke of this possibility in every school and asked the principal and teachers to look for symptoms and call the

attention of the school nurse and physician to every possible case. There were more than a thousand girls who took the full treatment, and only five developed any noticeable rash. None of these gave any trouble and the condition lasted only three or four days. Four of the girls continued the treatment and paid no attention to it, while the fifth asked to be excused from further treatment and the rash promptly cleared up.

As to the possibility of producing symptoms of Basedow's disease by giving iodin (in small doses) to a large number of girls indiscriminately, we can say that we have not seen a single instance in which any sign of such an effect was produced.

The earnestness with which the school girls have taken up the prophylaxis of goiter is encouraging for the practical application of this work. It is entirely elective on the part of the girls, and last year 1,080 girls finished the treatment. This year approximately 2,000 girls are taking the treatment.

SUMMARY

1. Simple goiter can be prevented by the administration of small amounts of iodin.

2. One third of the cases of uncomplicated simple goiter disappear or are markedly decreased by the use of a small amount of iodin, given internally.

3. There is no danger of producing a toxic condition ("Basedow's disease").

4. A very small proportion of the cases (at most 0.5 per cent.) may develop an iodid rash, which promptly clears up on stopping the treatment.

We wish to thank Prof. H. V. Hotchkiss (Superintendent of the Public Schools), the Board of Education and the Principals of the several schools; through whose excellent organization and system, as well as the interest in the problem, the work was made possible.

THE CLINICAL SIGNIFICANCE OF THE ABNORMALLY WIDE VENTRICULAR DEVIATION IN THE ELECTROCARDIOGRAM *

SELIAN NEUHOF, M.D.
NEW YORK

Electrocardiographic curves have given us exact and conclusive graphic records of many and varied types of cardiac arrhythmias. They have also offered some evidence, as yet inconclusive, regarding the presence of right and left ventricular hypertrophies. Furthermore, electrocardiograms have been of aid in diagnosing main branch lesions of the auriculoventricular conduction system; in isolated instances, the electrocardiographic diagnosis has been supported by pathologic examination of the heart. Because of the importance and clinical significance of myocardial disease, attempts are constantly being made to interpret the condition of the myocardium from the electrocardiogram.

In an electrocardiographic study of a series of patients with valvular, and with myocardial disease,[1] I have observed a characteristic which seems of importance in the diagnosis of myocarditis, namely, the abnormal width of the main deviation of the ventricular complex, commonly called the R-wave or the first ventricular spike. The width of the normal R-wave has been variously estimated. Hirshfelder[2] estimates it as 0.02 of a second; Lewis[3] as from 0.03 to 0.04 of a second. Though not directly mentioned by Einthoven[4] or Nicolai,[5] measurements of a number of their normal ventricular complexes give an average width of less than 0.05 second. All these measurements have reference to R-waves of normal form, that is, those that are neither split nor splintered, and whose sides form rectilinear lines which meet

*Submitted for publication Feb. 18, 1918.

1. The diagnosis, myocarditis, is often made on insufficient grounds; for example, on the presence of soft murmurs and presumed enlargement of the cardiac area to percussion. By myocarditis I mean severe pathologic damage to the myocardium, more often evidenced by hypertension, aortitis, precordial distress, decompensation and the probability of coronary disease, rather than by auscultatory signs. The term cardiosclerosis I mean to apply to clinical conditions in which, in addition to coronary and aortic disease, there are assumed to be thickening and degenerative changes of the valves and endocardium, in addition to myocarditis.

2. Hirshfelder, Diseases of the Heart, Ed. 2, p. 89.

3. Lewis: Heart, 1912-1913, **4**, 242.

4. Einthoven: Pflüger's Arch. f. d. ges Physiol., 1912, **63**, 152.

5. Nicoli, Handb. d. Allg. Path. u. Krankh. d. Herz u. Gefässe., **3**, Part 1, 137.

at a sharp angle and form a sharp apex. In the measurements of my cases I have included only clean-cut deviations of normal form. As an arbitrary standard in my series I have adopted a base line width of 0.07 or over as representing abormally wide deviations. From my own measurements of many ventricular deviations of patients with normal hearts, and from the normal standards of others, I believe that 0.07 of a second (or over) probably represents a deviation which has taken an abnormally long time for its completion. Indeed, in only one instance (M. G., Case 13) have I found the R-wave of a normal heart wider than 0.07 of a second.

Recently, Robinson[6] pointed out the clinical importance of abnormally wide and splintered ventricular complexes as evidence of marked functional changes in the heart. Oppenheimer and Rothschild[7] have shown that some cases of myocardial disease involving especially the subendocardial myocardium, present an R-complex of low voltage, wide base and irregular sides. They believe this occurs because myocarditis in this location interferes with the rapidity and uniformity of the spread of the electrical impulse through the heart by involving the superficial end branches of the conduction system. These observers have confirmed the deductions drawn from the electrocardiograms by the pathologic study of a number of necropsies. Eppinger and Rothberger[8] have induced experimental destruction of various parts of the cardiac musculature by freezing with ethyl chlorid, or by the injection of destructive substances. Electrocardiograms were taken before and after the injections. When, for example, a strong nitrate of silver solution was injected in the deeper layers of the left ventricle either at the base or apex, there was a marked change in the ventricular deviation. Within five minutes after the injection the descending limb became shorter so that it no longer touched the base line; this shortening became progressive so that in about twenty minutes the R and T deviations formed practically a monophasic curve. Injections of nitrate of silver in the superficial layers, or in the anterior or posterior papillary muscles were not followed by the foregoing changes in the electrocardiogram. Injections in the right ventricle were not regularly followed by electrocardiographic changes; the most typical consisted in a widening and prominence of the S and T deviations. I mention these experiments in some detail because they have an important bearing on the present clinical study. We must assume that we clinically meet with focal myocardial changes probably at times similar in loca-

6. Robinson, THE ARCHIVES INT. MED., 1916, **18,** 830.

7. Oppenheimer and Rothschild: Proc. Soc. for Exper. Biol. and Med., 1916, **14,** 57.

8. Eppinger and Rothberger, Wien. Klin. Wchnschr. 1909, **22,** 1091.

tion and destructiveness to the experimental lesions quoted; yet in only a single instance in a study of very many cases of marked cardiosclerosis did I observe an electrocardiogram which resembled that derived from Eppinger and Rothberger's experimental injection in the deeper layers of the left ventricle. It therefore seems unwarranted to draw deductions of the state of the pathologic process in the human heart from the type of experimental damage already quoted. This discrepancy may rest on the fact that the rapid experimental destruction of the myocardium produces some special change on the electrocardiogram, or that in almost every instance, in the human heart, where there are marked localized changes, there is also damage in other portions of the myocardium; that is, the local damage is only part of general myocardial disease.

In a description of cases assuming defective conduction in one of the main branches of the auriculoventricular bundle, Carter[9] describes as characteristics of these lesions, a Q-R-S time exceeding 0.10 second, increased amplitude of the R deflections, and T-waves, often exaggerated and usually in a direction opposite to that of the prominent initial deflection. The initial deflections themselves are very frequently atypical in form in at least one lead; bizarre forms are common. The assumption of branch bundle lesions in these cases has recently been questioned (Oppenheimer and Rothschild[10]).

In the cases that I report there has been no reason to assume an abnormal path for the impulse, for the electrocardiograms possess none of the characteristics of the aforementioned groups. Except for the abnormally wide base line, the electrocardiograms are of the usual normal types in form and size. Some of the deviations are tall. That amplitude in itself, however, need not necessarily imply an abnormally wide base is shown in Figure 12, in which R I is quite tall though of normal width.

A glance at the summary in the accompanying table of cases shows that, grouping them by their clinical characteristics, in all instances but two (Cases 3 and 5), there was grave disease of the myocardium; that is, myocarditis represented an important part of the clinical entity. The two exceptions were cases of rheumatic aortic disease, in both of which ventricular hypertrophy was extreme. That abnormal prolongation of the time of electrical impulse is not due to decompensation itself is evidenced by the fact, as noted in the clinical histories, that many of the electrocardiograms were taken when the patients were perfectly compensated. Ventricular dilatation per se as a cause for the abnormally wide R could be excluded. First, there was no evidence of

9. Carter, THE ARCHIVES INT. MED., 1914, **13,** 805.
10. Oppenheimer and Rothschild, Jour. Am. Med. Assn., 1917, **69,** 429.

any extreme dilatation, certainly not in the compensated cases. Secondly, in a study of a large series of cases of decompensated valvular lesions, in which cardiac dilatation was presumably a prominent feature, I found no abnormally wide R. Nor had I there found any correlation between hypertrophies—even extreme—and the width of the R deviation. Whether in the present study Cases 3 and 4 may be regarded as evidence of myocarditis in addition to hypertrophy, it is impossible to say.

TABLE 1.—Giving Data of Author's Cases

Case No.	Clinical Diagnosis	Rhythm	Width of R in Hundredths of a Second	Remarks
1	Myocarditis; coronary disease	Normal	RII =0.07 RIII=0.08	Arrhythmia and death
2	Luetic aortitis; myocarditis	Interpolated extrasystole	RI =0.12 RII =0.07 RIII=0.13	
3	Rheumatic aortitis	Auricular fibrillation	RII =0.07	Massive ventricular hypertrophy; death in one year
4	Cardionephritis	Normal	RI =0.08 RIII=0.08	Precordial pains
5	Rheumatic aortitis	Normal	RI =0.10 RII =0.09 RIII=0.08	Massive ventricular hypertrophy
6	Cardionephritis	Normal	RI =0.10 RIII=0.07	
7	Cardionephritis	Auricular fibrillation	RI =0.08	Died in uremia coma
8	Myocarditis; arteriosclerosis	Sinus arrhythmia	RI =0.08 RIII=0.08	
9	Aortic aneurism	Normal	RII =0.07	Moderate amount of myocarditis at necropsy
10	Cardiosclerosis	Auricular fibrillation	RII =0.08 RIII=0.09	
11	Cardiosclerosis	Normal	RI =0.12 RIII=0.08	Aneurismal dilatation of the aortic arch

It will be noted from the table that the electrocardiograms showed an abnormally wide R in one or two leads, rarely in all three. In view of the fact that the leads draw off the current from various cardiac areas—breadthwise in Lead I, diagonally in Lead II, and lengthwise in Lead III—one may possibly assume that the diseased myocardium lay more in one plane of the current than the other, thus interfering with the quick distribution and spread of the electrical current in that particular plane.

It remains to indicate this important fact that while the cases mentioned show abnormally wide ventricular deviations and are apparently

indicative of severe myocardial disease, I have observed cases clinically similar to the above with perfectly normal electrocardiograms. The reason for this is not at present apparent.

CONCLUSIONS

An arbitrary standard of 0.07 of a second was fixed as representing the lower limit of abnormally wide ventricular deviations which were otherwise normal in form and contour. Thus standardized, an abnormally wide R was found in a series of patients, all of whom, with two exceptions, showed evidence of marked myocarditis. These two were cases of rheumatic aortic disease, with extreme ventricular hypertrophy. The presence of the wide R seemed to indicate, though its absence did not exclude, myocarditis. It had no relation to the height of the R, the pulse rapidity, the cardiac rhythm, or to the underlying disease producing the myocarditis. In some of the cases, severe

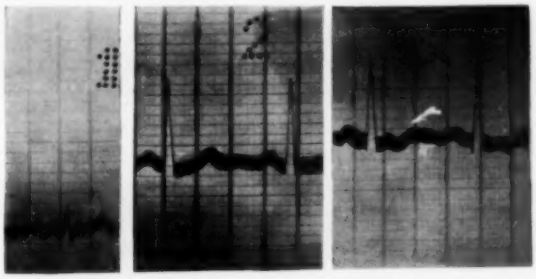


Fig. 1.—Electrocardiogram of A. G., Case 1. For description of this and tracings of following cases see the reports of cases from 1 to 11. In all the electrocardiograms the vertical lines measure 0.20 of a second.

decompensation was present; in others, it was absent. Though no definite statement of the fundamental cause of the abnormally long duration of the R phase can be offered, its frequent association with myocarditis would make it appear possible that this lesion acted as a direct hindrance to the proper normal, rapid propagation of the wave of electrical excitation through the ventricular musculature.

REPORT OF CASES

Case 1.—A. G., man, aged 54, had complained for two years of indefinite precordial pains radiating to the left hand, and of attacks of dizziness. He had been unable to work for several months because of these attacks. On examination, the systolic blood pressure was found to be 166, the diastolic 88. The first aortic sound was blurred, the second somewhat accentuated. The other heart sounds were normal. There was slight edema of the legs. The urine contained no albumin or casts. Fluoroscopic examination showed a normal sized aorta; the ventricular outline was somewhat enlarged to the left. The

electrocardiogram at that time (Fig. 1) showed normal rhythm; R II and R III were respectively 0.07 second and 0.08 second in width. The subsequent history of the patient was of interest. Following the use of digitalis and of theobromin sodium salicylate, there was gradual improvement in the symptoms for about one year. The patient then developed sudden attacks of tachycardia, each of which lasted several days. The symptoms during these attacks were mainly subjective and consisted in the uncomfortable recognition of the rapid heart action; dyspnea was slight. About one week after the last attack he suddenly complained of precordial distress, followed by faintness. The patient was moderately dyspneic. Auricular fibrillation with rapid ventricular activity was present. A diagnosis of coronary thrombosis was made. Five days after

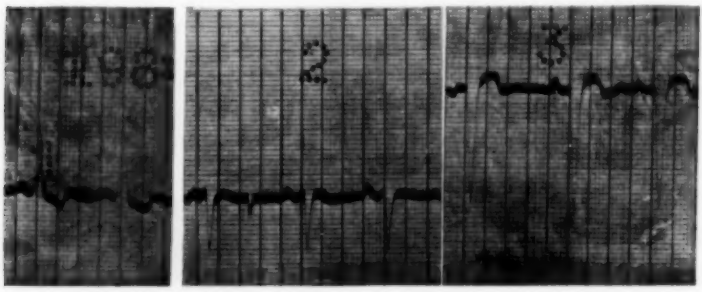


Fig. 2.—Tracing of W. Z., Case 2.

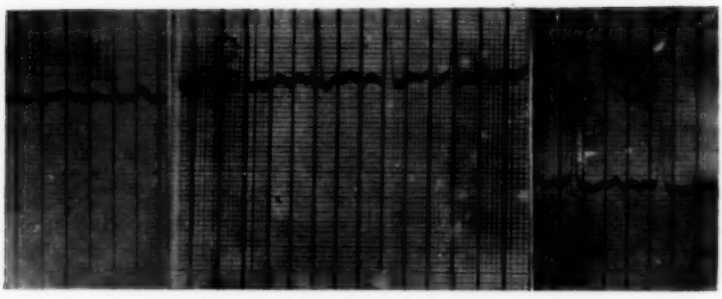


Fig. 3.—Tracing of H. Y., Case 3.

the onset of fibrillation, while sitting quietly on a chair and apparently quite comfortable, he suddenly gasped and died within a few minutes. The clinical diagnosis was myocarditis and coronary sclerosis.

Case 2.—W. Z., man, aged 57, entered the hospital with general anasarca and the usual symptoms of cardiac decompensation. This had been the third break of compensation within recent years. The physical signs revealed the presence of an aortitis and of left ventricular hypertrophy. This was corroborated by roentgenography, which showed in addition, aneurismal dilatation of the entire thoracic aorta, and ventricular enlargement which practically filled the lower left half of the chest. The Wassermann blood examination was 4+. On antisyphilitic treatment, Karrell diet, digitalis and theobromin

sodium salicylate, the patient quickly improved. The electrocardiogram (Fig. 2), taken when the patient was compensated, showed abnormally wide ventricular deviations in all leads, especially in the first and third; the R widths were respectively 0.12 and 0.13 second; R II was 0.07. The clinical diagnosis was syphilitic aortitis, myocarditis and left ventricular hypertrophy.

Case 3.—H. Y., man, aged 31, had acute articular rheumatism six years prior to admission. Six weeks prior he suffered from what at first appeared to be grip; this was soon followed by fever and joint pains. He had never had any cardiac symptoms until recently. Examination revealed markedly throbbing carotid, subclavian, brachial and radial arteries. A rough systolic thrill was heard over the carotid and over the aorta in the jugulum. There was a

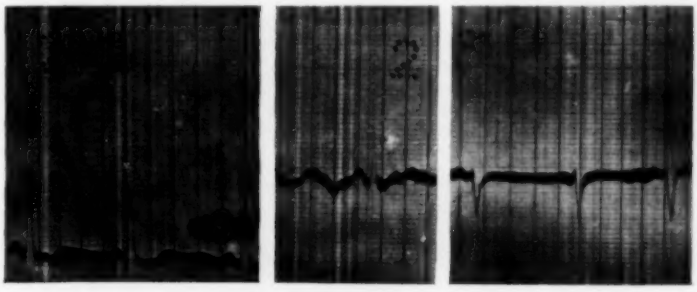


Fig. 4.—Tracing of I. K., Case 4.

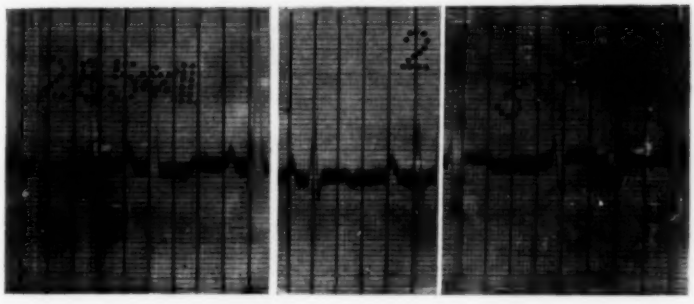


Fig. 5.—Tracing of E. O., Case 5.

loud, rough, double murmur over the right base. The liver was somewhat enlarged. The urine contained a trace of albumin and a few granular casts. The Wassermann blood examination was negative. The orthodiascope revealed an enlarged and hyperacting aorta, the left ventricle was moderately enlarged. The electrocardiogram (Fig. 3) showed auricular fibrillation; the width of R II was 0.07. The patient developed hemorrhagic erythema of the legs, and later, rheumatic joint manifestations. He died within three months. The clinical diagnosis was a double aortic lesion and moderate left ventricular hypertrophy.

Case 4.—I. K., woman, aged 57, complained for several years of a feeling of oppression in the chest and of numbness in the fingers of both hands.

There were also occasional attacks of nocturnal dyspnea accompanied by precordial pains. The systolic blood pressure ranged between 180 and 220, the diastolic between 90 and 110. There was a metallic second sound over the aorta, and a systolic murmur at the apex. With the fluoroscope, the aortic arch was found enlarged, the left ventricle moderately hypertrophied. The urine showed a trace of albumin and a few casts. R I and R III (Fig. 4) were each 0.08 second in width. The clinical diagnosis was cardionephritis.

Case 5.—E. O., woman, aged 21, had "growing pains" as a child. Her "heart trouble" began at the age of 10. The chief complaint was palpitation, especially after undue excitement. The systolic blood pressure was 180, the diastolic, 30 mm. The classical signs of a double aortic lesion and left ventricular hypertrophy were present. The orthodiascope revealed a violently pulsating aorta and massive ventricular hypertrophy, as well as enlargement of the cardiac shadow to the right. The electrocardiogram (Fig 5) showed the widths of the R deviations as follows: R I = 0.09 and R III = 0.08.

Case 6.—A. K., man, physician, aged 53, had scarlet fever at the age of 15. Since then he had had occasional traces of albumin and casts in his urine. Of late, he had become somewhat dyspneic. The systolic blood pressure ranged between 175 and 190, the diastolic between 110 and 85. The second

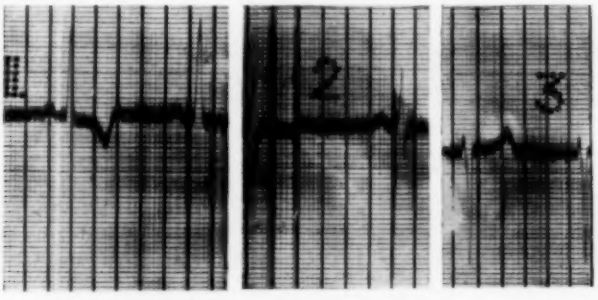


Fig. 6.—Tracing of A. K., Case 6.

aortic sound was somewhat accentuated; there was a systolic murmur at the apex. The liver was somewhat enlarged. The urine contained a trace of albumin, and granular and hyaline casts. There was slight edema of the legs. The blood Wassermann was negative. The orthodiascopic examination revealed a somewhat enlarged aorta and cardiac shadow. In the electrocardiogram (Fig 6), R I and R III were each 0.07 second wide. The clinical diagnosis was cardionephritis.

Case 7.—I. W.,[11] woman, aged 45, was brought to the hospital in a comatose condition. The only history obtainable referable to her present condition was that six years previously, when pregnant, she lost her eyesight (uremia ?); labor was induced and her eyesight returned. At the present examination the heart was found hypertrophied, there was marked accentuation of the second sound at apex and base. The systolic blood pressure was 270 mm. A blood culture was sterile. The electrocardiogram (Fig 7) showed that R I was 0.08. Two days after admission the patient died in uremic coma. The clinical diagnosis was cardionephritis.

---

11. I am indebted to the electrocardiographic department of the Post-Graduate Hospital for the privilege of reporting Cases 7 to 10, with their corresponding electrocardiograms.

Case 8.—S. M., man, aged 53. He complained for several years of dyspnea and precordial pains, particularly on slight exertion. He had had transient attacks of Cheyne-Stokes breathing; at such times his pulse was arrhythmic, electrocardiographic curves showed that the arrhythmia was of sinus origin. The apex was in the sixth left interspace, 14 cm. from the midsternal line. The heart sounds were faint, there was a soft systolic murmur at the apex and a slightly accentuated second sound at the base. The radial arteries were thickened and tortuous. The systolic blood pressure was 190 mm., the diastolic,

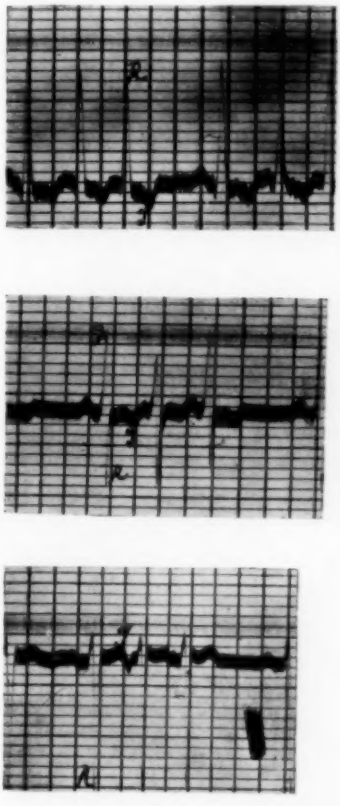


Fig. 7

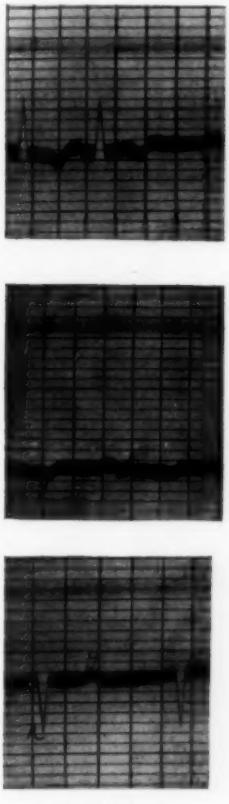


Fig. 8

Fig. 7.—Tracing of I. W., Case 7.
Fig. 8.—Tracing of S. M., Case 8.

110 mm. The electrocardiogram (Fig 8) showed that R I and R III were each 0.07 second wide. The clinical diagnosis was myocarditis and cardiosclerosis.

Case 9.—J. J., aged 53, man, had a very large, protuberant aneurysmal tumor the size of a large orange, situated at the upper right side of the chest. There were loud systolic and diastolic thrills and pulsations over the aneurysm.

there was also a systolic murmur and a systolic thrust at the cardiac apex. The apex was in the sixth interspace, 1 inch outside the nipple. Though the patient was somewhat dyspneic at first, there was no marked decompensation. R I and R III (Fig. 9) were each 0.07. The aneurysm was wired. After some weeks, there were frequent external hemorrhages from the aneurysmal sac; the patient gradually succumbed. At necropsy, besides the aneurysm, the ventricles were moderately hypertrophied and showed a moderate amount of myocarditis.

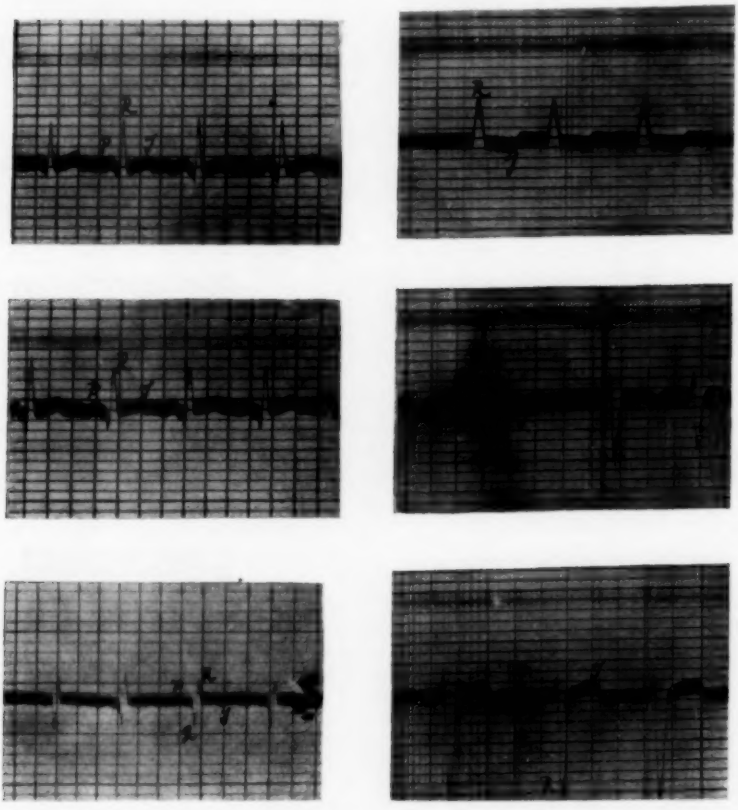


Fig. 9 Fig. 10

Fig. 9.—Tracing of J. J., Case 9.
Fig. 10.—Tracing of J. C., Case 10

CASE 10.—J. C., man, aged 60, was addicted to alcohol. During the previous two years, he had had several mild attacks of dyspnea and of edema of the legs; the last attack occurred one week prior to admission. The cardiac apex was in the fifth interspace, 12 cm. from the midsternal line. There was a blowing systolic murmur at the apex, the second sound at the base was impure and

slightly accentuated. The arteries were thickened. The electrocardiogram (Fig 10) showed auricular fibrillation; R II was 0.08 second, R III 0.09 second wide. The clinical diagnosis was cardiosclerosis.

Case 11.—M. M., aged 65, had rheumatism several years prior to admission. She had been somewhat dyspneic for several years; of late this symptom has become more marked. The first examination revealed mucous râles over the entire chest. There was a loud systolic murmur heard over the upper right chest, transmitted into the carotids and to the left of the scapula posteriorly.

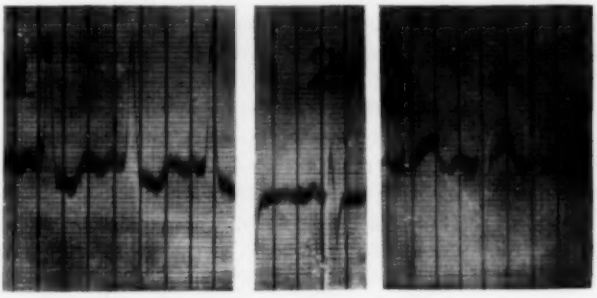


Fig. 11.—Tracing of M. M., Case 11.

Fig. 12

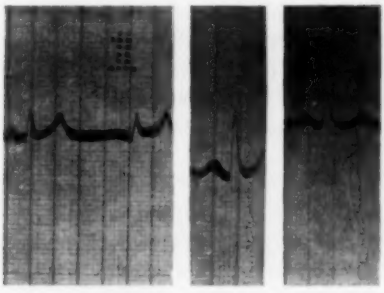


Fig. 13

Fig. 12.—Electrocardiogram of a patient with cardiosclerosis; tall R of normal width (R = 0.04).

Fig. 13.—Electrocardiogram of a patient with a normal heart and wide R. (R II = 0.08: R III = 0.08).

There was also a loud systolic murmur over the mitral area. The blood pressure was normal. There was slight edema of the legs. The urine showed a slight trace of albumin and a few casts. In the fluoroscope, there was found aneurysmal dilatation of the first portion and arch of the aorta; the heart was moderately enlarged. R I was 0.12 and R III 0.08 in width (Fig. 11). The clinical diagnosis was cardiosclerosis.

1275 Madison Avenue.

THE VALUE OF TESTS OF KIDNEY FUNCTION

A DISCUSSION OF KIDNEY FUNCTIONAL TESTS WITH ESPECIAL REFERENCE TO THEIR PROGNOSTIC VALUE *

LEWIS F. FRISSELL, M.D., AND KARL M. VOGEL, M.D.
NEW YORK

The use of the tests of kidney function has become so common a procedure in our hospitals in the past few years that little time need be wasted in recapitulating them. In general, four principles are involved:

1. The determination of the rate of excretion in the urine of a known amount of a chemical substance, injected or ingested.

2. The determination of the degree of retention in the blood of various normal metabolic products.

3. The comparison in a patient on a known test diet of the ingestion and excretion of nitrogen, sodium chlorid, water, etc.

4. A determination of the ratio between the concentration of various metabolic products, ordinarily urea, in the blood, and their excretion in the urine, the result being expressed as a ratio of excretion or coefficient.

Of the first group, the procedure most widely used is the phenolsulphonephthalein test of Rowntree and Geraghty, which determines the amount of the dye excreted in the urine during a two-hour period following the intramuscular injection of a definite amount. Indigocarmin is also used, and in a recent communication Thomas and Birdsall[1] say that they consider it more trustworthy than phenolsulphonephthalein.

Other tests are the lactose and potassium iodid tests used by Schlayer and Takayasu, as being analogous to the urea and sodium chlorid normally excreted. Theoretic objection to tests of this group may be made on the ground that the reaction of the kidney is tested to a foreign substance, and that normal metabolic products might and do show a different excretion rate.

In the second group, the concentration of the various nitrogenous constituents of blood has been particularly studied, and owing to the more recent methods of blood analysis introduced by Folin and Denis, Marshall, Van Slyke, Cullen, Benedict, and others, their determination has been rendered both easier and more accurate. Nonprotein nitrogen, urea nitrogen, uric acid, and creatinin have been the substances investigated, and much light has been thrown on the amounts normally present and their retention in pathologic conditions. Here, too, theo-

* Submitted for publication Feb. 19, 1918.
* From St. Luke's Hospital.
1. Thomas and Birdsall: Jour. Am. Med. Assn., 1917, **69**, 1747.

retical objection to the value of the tests may be made on the ground that they do not directly take into account the ingestion of fluid or protein, and that the concentration of the substance in question may be altered by either one of these factors; also, that the rate of excretion not being known, we do not know whether the concentration is being increased or diminished.

The third method, a study of the excretion of substances normally eliminated, mainly of the water, nitrogenous bodies, and salt, and the comparison of these with the amounts present in the diet is a procedure elaborated by Hedinger and Schlayer, and in the United States particularly studied by Mosenthal. This method, while having much to commend it, since the analytical procedures required are simple and there is a minimum of disturbance to the patient, is somewhat troublesome since it demands weighed diets and the accurate collection of numerous specimens of urine—not always an easy matter to secure in a general ward, as all of us who have had our struggles with careless orderlies realize only too well. The method further presupposes that the kidneys are the only factor in retention, which, as in the salt retention of pneumonia, we know is not always the case.

The fourth method, a comparison of the concentration of the salts, urea particularly, in the blood, with their excretion in the urine, the result being expressed as a formula, was suggested by Ambard, and the numerical result obtained is known as Ambard's coefficient. This coefficient expresses mathematically the ratio between the concentration of urea in the blood and its excretion in the urine, the normal numerical expression of which is 0.080, deficiency in function resulting in higher values.

At the time of Ambard's work in 1910, the determinations of urea in the blood were inaccurate and his formula was never widely used, but the present urease method of determining blood urea devised by Marshall and modified by Van Slyke, and the utilization of Ambard's law by McLean, have resulted in the latter's so-called index of urea excretion, which gives the more readily remembered numerical expression of 100 as a normal, with lower readings due to deficient kidney function. Very high readings, however, are sometimes encountered in normal individuals and the meaning of these high variations is obscure. Fortunately the fluctuations in the lower pathologic readings are not so frequent, though occasionally seen. This method has also the advantage of directly determining the blood urea, which forms one of the factors in the mathematical formula, and may be used for a check as a direct determination.

During the past three years there have been made in the chemical laboratory of St. Luke's Hospital numerous determinations covering the various forms of these tests. Of several thousand blood analyses

from many different types of cases, we wish to report only those made in definite cases of nephritis. Of these, the total number is 124, including over 1,500 separate tests, in most instances covering the complete series of analyses; that is, determination of McLean index, phenolsulphonephthalein excretion, urea nitrogen, and nonprotein nitrogen. As our work confirms that of others in that abnormal finding are rarely encountered when the kidneys are unaffected, we have rejected those cases in which the disturbance was purely cardiac, with congested kidneys, and also such conditions as pernicious anemia, pneumonia complicating nephritis, etc., in order to narrow our problem to nephritis per se.

This reduces our list to 112 patients, on whom over 1,400 observations were made, covering more or less completely the entire series of tests. As abnormal in the above sense, we took a phenolsulphonephthalein below 50, nonprotein nitrogen above 35, and urea nitrogen above 25 mg. per 100 c.c. For the upper limit of normal blood urea we adopted McLean's figure of 0.5 gm. per liter, and 80 as a urea index, so as to eliminate those cases only slightly deficient in function.

The phenolsulphonephthalein test was made according to the intramuscular technic of Geraghty and Rowntree. The nonprotein nitrogen, creatinin, and uric acid determinations were made according to the methods of Folin and Denis, with modifications introduced by Benedict and others. For the estimation of blood urea, Van Slyke and Cullen's modification of Marshall's urease method was employed. McLean's index of urea excretion was calculated according to his formula, the urine being collected over a seventy-two-minute period with the specimen of blood taken at the midperiod, thirty-six minutes.

By means of correspondence and the visiting nurse an effort was made to follow up the patients and find out about the present condition of all who had left the hospital alive. Of the 112 persons with nephritis, showing findings of abnormal kidney function, sixty-nine, or 61.6 per cent., died in the hospital or after leaving the institution. Twenty-four, or 21.4 per cent., were still living in varying conditions of health on the first of July, 1917, while nineteen patients, or 16.9 per cent., could not be traced. In general, the results given by all these tests are strikingly consistent, and the high percentage of fatal cases, 61 per cent., in a series of 112, is in accord with the indications furnished by the functional tests.

An effort was made to record graphically the course of renal function from the time of first observation to the time of death (Fig. 1). Our sixty-nine fatal cases are, of course, far too few to give a really accurate representation of such a curve, but as in many of them we have observations extending over a period of weeks or months, in one case over two years, the resulting curves, based on 685 separate determinations, are at least suggestive. The number of observations is, of

course, far in excess of the number of patients, and particularly in the case of phenolsulphonephthalein, blood urea, and the urea index, sufficiently large to be of value during the last three months of the patient's life.

The figures on uric acid and creatinin, except during the last two weeks of life, are too few to be of much statistical value. At this period they are uniformly high. The average shown by the curves of phenolsulphonephthalein, nonprotein and urea nitrogen, and the urea index, seems to indicate a method which, if checked by a large number of

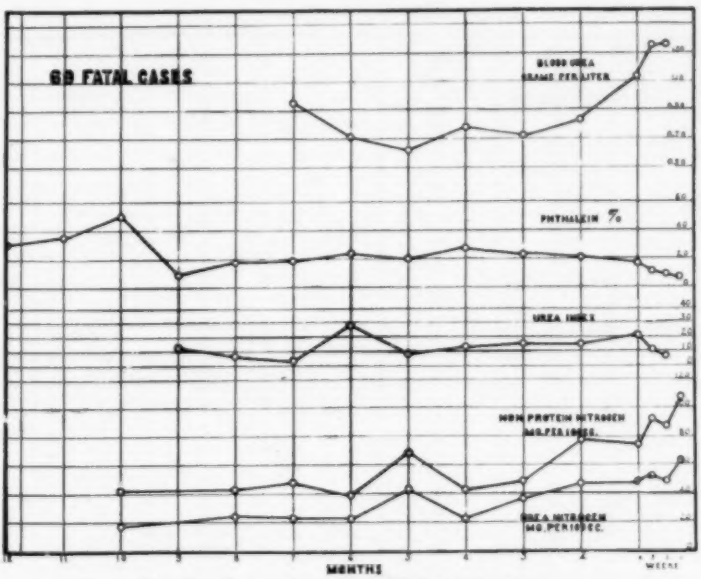


Fig. 1.—Curves based on 685 determinations.

observations, might prove valuable in arriving at an average expectation of life for a given determination.

The curves for the nonprotein nitrogen and urea nitrogen show a rapid rise during the three months preceding death, while during the earlier months there is a tendency for the curves to maintain a constant level. The elevation at the fifth month which disturbs the symmetry of the curves is caused by a single case in which the values were so high that the averages were disproportionately raised.

Many individual patients of course will have high retention values and still continue to live, as in the case of No. 110,796 (Fig. 3) who, five months after showing such figures as nonprotein nitrogen 160, urea index and phenolsulphonephthalein close to 0, was still living. Others

with normal values will die of uremia, for this high retention of normal substances is but the expression of abnormal function, and we must not blind ourselves to the fact that the actual poison in uremia is unknown, and that we have no test which expresses either its retention, or rate of excretion; yet, in the long run, the higher retention values and the lower excretion ratios indicate a kidney functionally so damaged as to be incompatible with life.

A second chart, based on 450 determinations, has been prepared showing the averages of those cases still living July 1, 1917 (Fig. 2). This of course has not the value of the first, and the curves show great

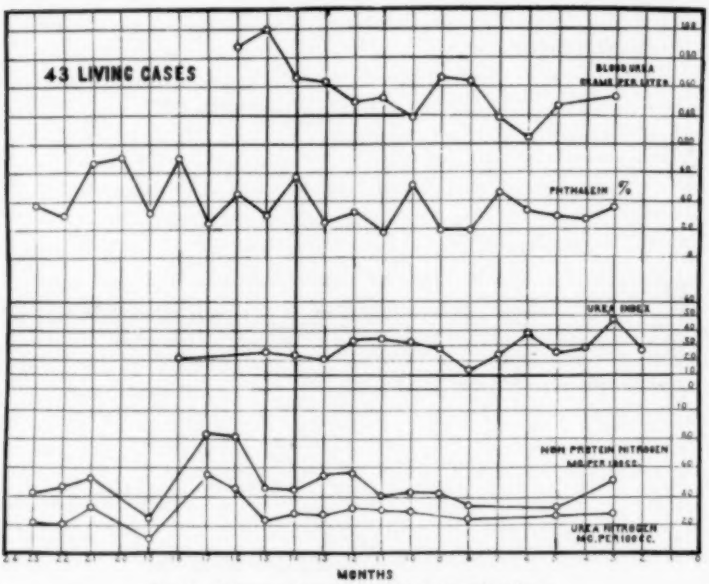


Fig. 2.—Curves based on 450 determinations.

irregularity. As an arbitrary date, July 1 was selected as the terminal point, and the series probably includes cases shortly to prove fatal, but the error tends toward the inclusion of abnormal rather than of normal values.

One patient, 112,766 (Fig. 4), the course of whose disease was followed for over three years, showed in her phenolsulphonephthalein tests this impaired kidney function, her reading in 1913 being only 32 per cent. She continued for many months with headache, slight hypertension, and urine of a specific gravity of 1.012 to 1.015, occasionally exhibiting slight exacerbations, showing the long period of time over which severe functional incapacity of the kidney may exist until death finally ensues.

Jonas and Austin[2] have criticized the McLean index on the ground that the blood urea determinations are much easier in technic and equally valuable. In support of this contention, the authors cite their series in which only two cases appeared in which the index was abnormal and the blood urea normal. They state correctly that some difference of opinion exists as to what constitutes an abnormal blood urea, McLean's[3] belief being that the normal range extends from 0.2 to 0.5 gm. per liter, while Tileston and Comfort[4] give 0.25 to 0.34 as normal limits. In our series 246 determinations show abnormally low indexes.

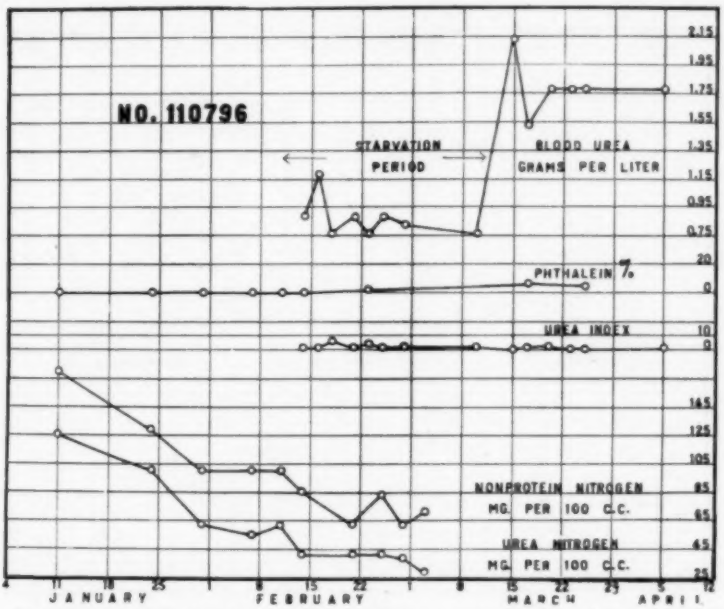


Fig. 3.—Note diminution in blood nitrogen retention during starvation period without alteration in phenolsulphonephthalein output or urea index. The record also illustrates the extreme retention values rarely seen over long periods.

Taking Tileston's normal as correct, thirty-nine, or just under 15 per cent., had normal blood urea values, while eighty-six, or 33.2 per cent., were within the normal range, if McLean's contention be correct. Our results therefore seem to prove that the delicacy of the index of urea excretion is much greater than that of a simple blood urea determina-

2. Jonas and Austin: Am. Jour. Med. Sc., 1916, **152,** 560.
3. McLean: Jour. Exper. Med., 1915, **22,** 212.
4. Calculated from values of urea nitrogen given by these authors in THE ARCHIVES INT. MED., 1914, **14,** 620.

tion. Fifteen to 33 per cent. is far too great a discrepancy to disregard. McLean[5] has recently published two cases in which the state of urea excretion was studied at different levels of protein metabolism. These observations confirmed those of Widal and Javal and showed that the state of the function of urea excretion remained unchanged even though great alterations in the concentration of urea in the blood took place.

As a means of following the effect of diet, diuretics, etc., these methods have a very real value. Take for instance the chart of No. 110,796 (Fig. 3), a sufferer from chronic interstitial nephritis with

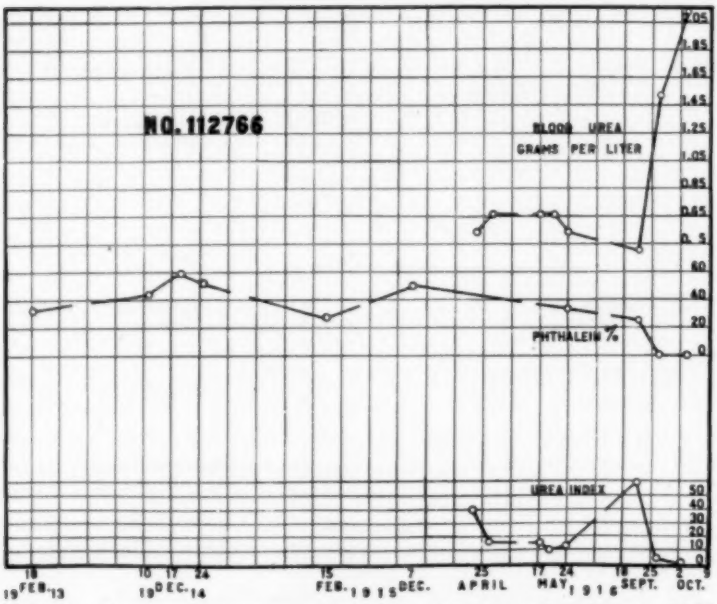


Fig. 4.—Showing the average type of case of moderate impairment of kidney function of several years' duration, with sudden rise in retention values and fall in phenolsulphonephthalein output during the last weeks of life.

convulsions. This patient was kept from February 11 to March 11 on a diet extremely low in nitrogen, at times containing almost no protein, and never above 30 gm. The amount of blood urea on this diet fluctuates between 0.7 and 1.1 gm. per liter, while on the resumption of a diet containing approximately 50 to 75 gm. of protein the figures are raised to 1.55 to 2.1 gm. per liter. Neither the urea index nor the phenolsulphonephthalein, however, rose during this starvation period, and the

5. McLean: Jour. Am. Med. Assn., 1917, **69**, 437.

patient's condition, in spite of her improved blood urea retention, and her extreme nitrogen starvation, did not change materially. She left the hospital against advice and six weeks later was found by the visiting nurse in about the same condition, but it has been impossible to ascertain the subsequent course of her case. The results of the tests in this instance also illustrate the value of the index as compared with the simple determination of the blood retention products.

On the other hand, the improvement of Patient 111,478 (Fig. 5) with a chronic diffuse nephritis, abundant albumin and casts, and with a ++++ Wassermann accompanying a possible syphilitic nephritis is shown following the administration of a single dose of arsenobenzol after a preliminary period during which his tests, particularly his

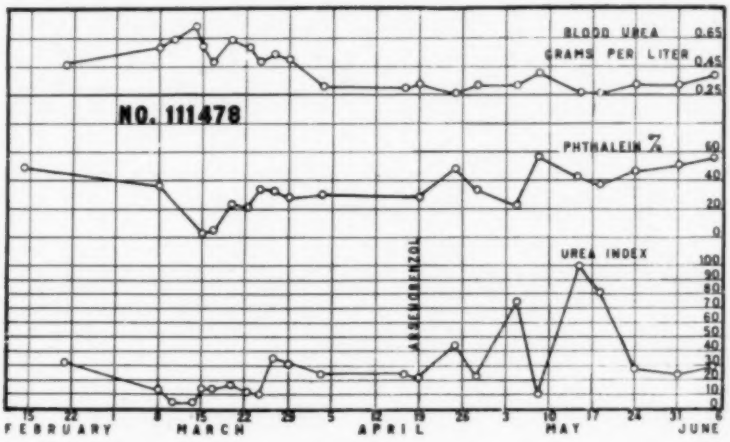


Fig. 5.—Chart of a fatal case showing temporary improvement after administration of the arsenobenzol brand of arsphenamin.

salt balance, were much impaired. The improvement was gradual, lasting until his discharge from the hospital, but it was subsequently learned that he died two months later.

In conclusion, it may be said:

1. The kidney functional tests have a real prognostic value, particularly if the results are constantly abnormal on repeated examination.

2. The higher values for the blood retention products are found mainly in the terminal stage.

3. By plotting the curve of a very long series of cases it should be possible to arrive at an average expectation of life as indicated by any individual determination.

4. The value of diet and drugs may in the future be shown more clearly by these methods than by any others now available.

TABLE 1.—FINDINGS IN SIXTY-NINE FATAL CASES

Case No.	Age	Sex	Date of Examination	Phenolsulphonephthalein, per Cent.	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Date of Death	Fundus	Diagnosis
					Mg. per 100 C.c.				Gm. per L. Blood Urea			S.	D.			
					Nonprotein N	Urea N	Uric Acid	Creatinin								
105912	45	♂	3/27/15	41.0	....	....	...	...	.....	....	1.010-15	275	160	8/ 9/15	.....	C. I. N.; uremia
			4/28/15	....	40.5	22.2										
			6/11/15	28.8	32.5	16.2	2.5									
			7/ 6/15	28.0	43.8											
106720	59	♂	6/ 8/15	....	53.0	26.5	...	...	.....	....	1.015-20	160	120	9/18/15	Negative	C. I. N.; carditis
			6/12/15	34.7												
106820	53	♀	6/26/15	58.0	31.0	....	...	...	.....	....	1.010-20	200	110	9/ 7/15	Negative	C. I. N.
			7/ 1/15	43.0												
			8/ 4/15	61.0	66.0	31.0										
106861	46	♂	6/15/15	27.5	54.0	24.7	...	...	.....	....	1.010	230	125	1/ 4/16	.....	C. I. N.; gout
			6/29/15	....	....	....	6.7									
107258	45	♂	7/ 5/15	Trace	50.0	33.0	...	...	.....	....	1.010	250	210	7/14/15	Negative	C. I. N.; uremia
107485	53	♀	7/17/15	25.0	43.0	22.0	...	...	.....	....	1.010-20	300	240	9/30/15	.....	C. I. N.
107910	36	♂	8/ 9/15	17.0	50.0	27.0	...	...	.....	....	1.005-20	205	150	8/16/15	Retinitis	C. I. N.
108213	43	♂	8/27/15	5.0	125.0	63.0	4.1	...	.....	....	1.015	240	140	9/ 7/15	.....	C. I. N.; uremia
			9/ 5/15	Trace	250.0	145.0	11.0									
108358	42	♀	9/ 6/15	41.7	45.0	25.0	6.2	...	.....	....	1.020-25	120	90	9/17/15	Negative	C. I. N.
			9/15/15	3.3	66.0	36.0										
108456	44	♀	8/ 2/15	14.5	63.0	31.0	...	...	.....	....	1.010-20	260	155	10/18/15	.....	C. I. N.
			9/13/15	Trace	111.0	83.0	7.1									
			9/22/15	Trace	73.0	50.0	7.6									
			9/27/15	Trace	106.0	62.5	8.3									
			10/ 4/15	....	117.0	71.0	7.1									
			10/11/15	Trace	100.0	22.0	10.9									
108527	53	♀	9/13/15	9.6	91.0	71.0	3.8	...	.....	....	1.010	200	120	9/23/15	Negative	C. I. N.; uremia
			9/17/15	14.0	77.0	60.0	6.2									
			9/22/15	....	118.0	62.5	8.3									
108710	56	♀	9/22/15	18.2	59.5	35.5	7.1	...	.....	....	1.015-20	...	...	9/28/15	.....	C. I. N.; uremia
108816	40	♀	9/27/15	Trace	125.0	82.5	...	...	.....	....	1.010-20	275	185	10/ 5/15	Retinitis	C. I. N.
109632	43	♂	5/28/15	5.16	53.0	21.7	...	...	.....	....	1.020-25	135	125	12/ 3/15	Negative	C. I. N.
			8/25/15	62.5	45.0	22.0										
			11/17/15	22.0	25.0	15.0										
109726	70	♂	11/16/15	Trace	112.0	83.0	...	...	.....	....	1.030	260	160	11/20/15	Negative	C. I. N.

110276	32	♂	12/13/15	....	100.0	71.5	5.0	...	.....	....	1.015	180	110	12/15/15	Negative	Acute N.; HgCl poisoning
110311	75	♀	12/17/15	....	55.5	27.7	...	...	.....	....	1.025	200	100	12/23/15	Negative	C. I. N.; cerebral hemorrhage
110435	53	♀	12/22/15	....	200.0	125.0	11.2	...	.....	....	1.010-25	220	100	12/22/15	Negative	C. I. N.; uremia
110501	58	♂	12/29/15	20.6	49.5	31.7	0.5	...	.....	....	1.010-25	235	115	7/ 5/16	.....	C. I. N.; carditis
			1/ 4/16	4.6												
			1/ 8/16	10.0												
110566	72	♂	12/29/15	41.7	54.5	31.7	...	...	.....	....	1.005	170	105	2/26/17	.....	C. I. N.
110858	68	♀	1/12/16	15.1	71.5	50.0	...	...	.....	....	1.005-15	260	140	2/ 7/16	Hemorrhage	C. I. N.; cardiac; uremia
			1/24/16	15.7	67.0	50.0										
			1/31/16	Trace	143.0	100.0										
111112	58	♂	1/28/16	Trace	100.0	71.5	...	...	.....	....	1.010-15	230	130	3/ 3/16	Retinitis	C. I. N.
			2/ 4/16	Trace	100.0	62.5										
			2/ 9/16	Trace	83.5	54.2	3.5									
			2/11/16	Trace	83.5	50.0										
			2/14/16	....	....	....	...	...	1.337	1.36						
			2/16/16	....	....	....	...	...	1.530	1.5						
			2/18/16	....	....	....	...	...	1.337	0.9						
			2/21/16	....	....	....	...	...	1.123	3.2						
111477	60	♀	2/14/16	....	38.0	20.8	3.1	...	.....	....	1.005-20	230	120	10/16/16	Retinitis	C. I. N.; uremia
			2/16/16	21.7	30.0											
			2/28/16	....	41.7	27.5	3.8									
			3/10/16	....	....	....	...	...	0.882	6.3						
			5/ 3/16	....	100.0	62.5										
			8/ 7/16	0	....	....	...	...	0.892	2.3						
			9/25/16	....	100.0	55.5										
			9/18/16	....	....	....	...	1.3								
111478	50	♂	2/14/16	49.0	37.0	25.0	...	...	.....	....	1.005-20	205	130	8/12/16	.....	C. I. N.
			2/21/16	....	....	....	...	...	0.445	31.5						
			3/ 8/16	36.2	....	....	...	...	0.535	14.5						
			3/10/16	....	....	....	...	...	0.595	4.2						
			3/13/16	....	....	....	...	...	0.667	4.3						
			3/15/16	4.5	....	....	...	...	0.535	14.4						
			3/17/16	5.6	....	....	...	...	0.434	14.2						
			3/20/16	23.0	....	....	...	...	0.592	17.0						
			3/23/16	21.7	....	....	...	...	0.535	11.4						
			3/25/16	33.3	....	....	...	...	0.445	10.5						
			3/27/16	32.0	....	....	...	...	0.481	35.0						
			3/29/16	28.6	....	....	...	...	0.453	31.0						
			4/ 3/16	30.0	....	....	...	...	0.269	24.7						
			4/16/16	30.5	....	....	...	...	0.256	24.0						
			4/19/16	28.5	....	....	...	...	0.280	21.5						
			4/24/16	48.2	....	....	...	...	0.214	44.5						
			4/28/16	33.8	....	....	...	...	0.267	22.5						
			5/ 5/16	22.2	....	....	...	...	0.268	75.0						
			5/ 8/16	56.7	....	....	...	...	0.357	10.0						
			5/15/16	41.7	....	....	...	...	0.214	100.0						
			5/19/16	37.5	....	....	...	...	0.214	82.0						
			5/24/16	46.2	....	....	...	...	0.262	27.0						
			5/31/16	51.0	....	....	...	...	0.261	24.0						
			6/ 7/16	55.6	....	....	...	...	0.346	29.0						

TABLE 1.—Findings in Sixty-Nine Fatal Cases—(*Continued*)

Case No.	Age	Sex	Date of Examination	Phenolsulphonephthalein, per Cent.	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Date of Death	Fundus	Diagnosis
					Mg. per 100 C.c.				Gm. per L. Blood Urea			S.	D.			
					Nonprotein N	Urea N	Uric Acid	Creatinin								
111480	44	♀	2/14/16	....	143.0	83.0	...	...	.....	....	1.005-20	132	70	2/19/16	.....	C. I. N.; carditis
111567	48	♀	2/23/16	....	35.7	....	...	...	.....	....	1.015-25	210	90	5/14/16	Negative	C. I. N.; uremia
			4/14/16	50.0	....	....	...	...	0.321	47.0						
			4/21/16	....	....	....	...	...	0.315	68.0						
111590	16	♂	9/15/15	31.3	33.0	11.0	3.1	...	.....	....	1.010-20	120	75	4/ 9/16	Negative	C. I. N.
			2/23/16	Trace	56.5	35.7	3.0									
			3/ 8/16	Trace	122.6	62.5										
			3/13/16	....	....	....	...	...	1.780	1.6						
112479	71	♂	4/16/16	....	100.0	50.0	...	...	.....	....	.....	...	...	4/16/16	.....	C. I. N.
112523	78	♂	4/16/16	43.3	28.5	15.0	5.0	...	0.383	27.5	.....	165	100	10/ 5/16	.....	C. I. N.
112756	33	♂	4/26/16	40.0	....	....	...	...	0.530	8.0	.....	200	165	4/23/17	.....	Pyelitis
			5/ 1/16	30.8	....	....	...	...	0.535	30.0						
112766	17	♀	2/18/13	32.0	....	....	...	...	.....	....	1.001-20	242	164	10/28/16	.....	C. D. N.
			12/11/14	44.5												
			12/21/14	59.4												
			12/25/14	52.4												
			2/15/15	27.9												
			12/ 7/15	50.3	....	....	...	...	0.535	40.0						
			4/26/16	....	....	....	...	...	0.667	16.0						
			5/17/16	....	....	....	...	...	0.668	15.0						
			5/19/16	....	....	....	...	...	0.667	10.0						
			5/24/16	35.0	....	....	...	...	0.535	13.0						
			9/ 4/16	....	111.1	55.5										
			9/21/16	25.0	....	....	...	...	0.405	54.1						
			9/27/16	0	....	....	...	...	1.526	4.25						
			10/ 4/16	0	....	....	...	...	2.140	0.8						
			10/14/16	Trace	....	....	6.09									
			10/27/16	....	167.0	83.3	...	2.9								
112805	35	♀	4/28/16	51.4	....	....	...	...	0.667	24.5	1.010-15	230	150	6/19/16	Hemorrhages	C. I. N.; uremia
			5/ 8/16	48.3	....	....	...	...	0.667	23.0						
			5/19/16	23.6	....	....	...	...	0.667	12.0						
			6/ 5/16	9.0	....	....	...	...	1.070	7.0						
112928	63	♂	5/ 1/16	....	30.0	14.0	4.54	1.0	.....	....	1.010-25	150	120	5/10/16	.....	C. I. N.; uremia
113021	48	♀	5/ 3/16	....	....	....	...	...	1.070	6.0	1.010-20	260	160	6/ 3/16	.....	C. I. N.; uremia
			5/ 5/16	10.0	....	....	...	...	0.934	46.0						
			5/15/16	7.1	....	....	...	...	1.187	2.8						
			5/22/16	....	92.0	50.0										

113560	47	♂	5/29/16	Trace	90.9	41.8	...	...	.....	....	1.010-20	...	...	6/ 7/16	.....	C. I. N.; uremia
			6/ 2/16	....	85.0	41.8	...	2.0								
			6/ 7/16	....	130.4	83.5	...	3.4								
113727	52	♂	6/ 7/16	....	56.0	31.2	...	...	.....	....	1.020	150	75	6/ 8/16	.....	C. I. N.
113779	58	♂	6/ 9/16	7.0	....	....	...	...	0.764	17.0	1.005-30	225	150	8/22/16	Retinitis	C. I. N.
			6/23/16	....	62.5	35.7										
			7/ 3/16	11.4	....	....	...	...	1.075	5.5						
			7/28/16	....	63.0	35.7										
113803	43	♀	6/12/16	....	45.5	35.7	...	...	.....	....	1.020	260	150	6/13/16	.....	C. I. N.; cerebral hemorrhage
114035	66	♀	6/26/16	12.5	38.5	22.7	...	1.4	0.535	12.0	1.005-20	260	115	6/ 5/17	Hemorrhages	C. D. N.
			6/30/16	22.2	33.5	20.7										
			7/24/16	....	....	....	...	...	0.411	30.0						
114416	29	♂	7/14/16	....	62.5	41.7	...	...	.....	....	1.015	136	94	7/16/16	.....	C. D. N.
114535	32	♀	7/19/16	21.1	....	....	...	...	0.535	23.0	1.001-20	220	150	10/22/16	Retinitis	C. I. N.
			7/26/16	....	38.5	27.8	5.5	1.6								
114562	68	♂	7/21/16	....	40.0	27.7	...	...	.....	....	1.010-20	155	105	8/ 7/16	.....	C. I. N.
			7/28/16	38.5	....	....	...	...	0.594	23.0						
114812	26	♂	4/12/16	11.8	....	....	...	...	0.445	4.7	1.010-30	190	165	1/ 8/17	.....	C. P. N.
			5/ 1/16	17.1	....	....	...	...	0.486	8.5						
			5/ 5/16	14.3	....	....	...	...	0.321	14.0						
			5/19/16	10.8	....	....	...	...	0.535	5.0						
			6/ 2/16	....	....	....	...	...	0.667	3.0						
			7/ 3/16	Trace	....	....	...	...	0.764	8.5						
			7/10/16	Trace	....	....	...	...	0.670	6.0						
			8/ 9/16	0	....	....	...	...	0.595	2.5						
			9/13/16	0	....	....	...	...	0.595	8.2						
			10/ 4/16	0	....	....	...	...	0.713	2.5						
			10/11/16	0	....	....	...	...	0.930	3.0						
			10/20/16	0	....	....	...	...	0.973	2.0						
			10/27/16	0	....	....	...	...	0.823	3.0						
			11/ 3/16	Trace	....	....	...	...	0.764	2.0						
			11/10/16	0	....	....	...	...	0.669	2.0						
			11/15/16	Trace	....	....	...	...	0.892	1.0						
			12/ 1/16	0	....	....	...	...	1.190	0.7						
			1/ 1/17	0	143.0	83.3										
114842	56	♀	8/14/16	13.2	....	....	...	...	0.669	4.5	1.010-30	225	125	1/14/17	.....	C. I. N.
114962	71	♂	5/12/16	27.2	....	....	...	...	0.607	6.5	1.010-15	165	80	8/15/16	.....	C. I. N.; uremia
			5/29/16	27.8	....	....	...	...	0.445	15.0						
115255	51	♂	9/ 6/16	....	83.0	50.0	...	2.0	.....	....	.....	105	80	9/ 5/16	.....	C. D. N.
115261	46	♀	9/ 4/16	32.0	....	....	...	...	0.357	34.0	1.010-40	185	125	11/ 9/16	.....	C. I. N.
115340	36	♂	9/25/16	20.7	....	....	...	...	0.384	13.2	1.010-20	210	140	9/27/16	.....	C. I. N.
115612	56	♂	9/25/16	50.0	....	....	...	...	0.629	23.5	1.005-20	190	140	1/ 9/17	.....	C. P. N.
115643	62	♀	9/27/16	37.5	....	....	...	...	0.713	20.0	1.010-30	185	75	10/22/16	Negative	C. D. N.

TABLE 1.—Findings in Sixty-Nine Fatal Cases—(*Continued*)

Case No.	Age	Sex	Date of Examination	Phenolsulphonephthalein, per Cent.	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Date of Death	Fundus	Diagnosis
					Mg. per 100 C.c				Gm. per L. Blood Urea			S.	D.			
					Nonprotein N	Urea N	Uric Acid	Creatinin								
115089	29	♂	10/16/16	0	....	....	...	...	1.070	3.3	1.005-20	220	150	12/ 5/16	.....	C. D. N.; uremia
			11/20/16	0	....	....	...	...	1.780	0.95						
116117	75	♂	10/23/16	36.4	....	....	...	...	0.892	24.0	1.005-20	235	135	11/10/16	.....	C. I. N.
			11/ 1/16	....	62.5	33.3	5.5	1.0								
116673	47	♀	11/20/16	45.5	....	....	...	...	0.973	6.5	1.005-30	175	75	12/ 9/16	.....	C. I. N.
117026	41	♀	12/ 7/16	40.0	31.3	16.1	5.0	0.8	.....	....	1.005-20	124	94	1/ 9/17	.....	C. I. N.
117248	58	♂	12/21/16	35.7	....	....	...	...	0.630	17.4	1.015-25	210	70	2/ 1/17	.....	C. I. N.; carditis
117317	47	♀	8/14/16	21.4	....	....	...	...	0.446	12.5	1.010-25	210	110	1/19/17	.....	C. I. N.
			8/28/16	12.5	38.5	25.0	8.9									
117437	24	♀	1/ 3/17	6.7	....	....	...	...	0.713	8.5	1.005-20	220	160	3/27/17	Retinitis	C. P. N.
			1/22/17	4.0	....	....	...	...	0.714	7.0						
			2/12/17	0	....	....	...	...	1.190	2.0						
			2/23/17	....	125.0	83.3	5.6	2.5								
			3/ 9/17	....	125.0	83.5										
117441	20	♂	1/26/16	53.0	50.0	27.8	...	...	.....	....	1.010	175	100	2/13/17	.....	C. I. N.
			2/ 7/16	37.2	62.2	38.5										
			2/25/16	....	50.0	31.2	...	...	0.667	22.5						
			2/28/16	49.0	50.0	25.0	...	...	0.535	23.5						
			3/ 1/16	....	....	....	...	...	0.507	26.3						
			3/ 3/16	....	....	....	...	...	0.667	21.6						
			3/ 6/16	....	....	....	...	...	0.764	18.1						
			3/ 8/16	38.8	....	....	...	...	0.759	18.4						
			3/10/16	....	....	....	...	...	0.667	21.2						
			3/13/16	....	....	....	...	...	0.764	14.5						
			3/15/16	46.8	....	....	...	...	0.753	24.5						
			3/17/16	....	....	....	...	...	0.667	17.4						
			12/ 6/16	....	....	66.7										
			1/ 1/17	43.0	....	....	...	...	1.338	8.4	1.008-20	220	110	7/25/17	Albuminuric retinitis	C. D. N.
117448	35	♀	1/ 1/17	25.0	....	....	...	...	0.715	5.5						
			1/10/17	10.0	....	....	...	...	0.800	6.0						
			1/17/17	15.6	....	....	...	...	0.972	9.0						
			1/31/17	7.0	....	....	...	...	1.070	5.0						
			2/ 9/17	....	....	....	...	...	0.821	32.0						
			2/28/17	15.0	....	....	...	...	0.646	7.5						
			3/ 7/17	20.0	....	....	...	...	0.790	8.0						
			3/30/17	13.0	....	....	...	...	0.860	8.0						
			4/20/17	15.7	....	....	...	...	1.130	5.0						
			6/ 8/17	8.0	....	....	...	...	1.340	2.4						
			7/ 2/17	21.4	....	....	...	...	1.785	1.5						
			7/ 6/17	....	111.0	66.8	...	1.8								

117995	53	♂	1/10/17	3.9	....	....	...	...	0.972	6.5	1.010-15	190	90	2/17/17	.....	C. I. N.
			1/17/17	4.9	....	....	...	...	1.258	3.5						
			1/31/17	0	....	....	...	...	2.140	2.0						
			2/ 7/17	0	....	....	...	...	2.140	2.0						
117649	29	♀	2/ 7/16	92.9	31.2	15.0	...	...	.....	....	1.010-15	175	140	1/27/17	Hemorrhages	C. I. N.
			1/10/17	14.0	....	....	...	...	1.070	6.7						
118219	53	♂	2/16/17	55.6	....	....	...	...	0.355	49.0	1.010-25	195	120	5/20/17	.....	C. I. N.; uremia
118556	20	♀	10/16/16	6.0	....	....	...	...	0.764	47.0	1.005-20	185	130	7/11/17	Sclerosis of vessels	C. P. N.
			10/27/16	11.6	....	....	...	...	1.070	7.0						
			11/ 6/16	10.0	....	....	...	...	0.972	3.2						
			11/22/16	23.0	....	....	...	...	1.338	0.15						
			12/ 1/16	17.8	....	....	...	...	1.427	5.0						
			12/16/16	12.0	....	....	...	...	1.427	0.15						
			12/21/16	....	....	....	...	...	1.190	0.15						
			1/ 3/17	7.5	....	....	...	...	1.070	7.4						
			1/12/17	5.2	....	....	...	...	1.070	5.6						
			1/22/17	6.5	....	....	...	...	1.070	4.3						
			3/ 2/17	Trace	....	....	...	...	1.528	1.1						
			3/ 7/17	9.1	....	....	...	...	1.530	2.0						
			3/14/17	9.0	....	....	...	...	1.070	5.6						
			3/28/17	8.3	....	....	...	...	1.190	3.7						
			4/20/17	5.0	....	....	...	...	1.130	5.0						
			6/11/17	4.0	....	....	...	...	1.070	2.7						
			6/20/17	0	....	....	...	...	1.340	2.9						
119166	46	♀	6/28/16	41.7	....	....	...	...	0.592	26.0	1.010-15	222	152	5/ 1/17	Negative	C. I. N.
			4/ 4/17	60.0	....	....	...	...	0.335	150.0						
			4/23/17	....	26.4	14.7										
119342	42	♂	4/13/17	2.0	....	....	...	...	1.070	10.0	1.010-15	230	160	5/ 8/17	Retinitis	C. I. N.; uremia
			4/20/17	3.0	....	....	...	...	1.530	2.0						
			5/ 1/17	....	....	100.0										
119523	34	♂	3/14/17	3.3	....	....	...	...	0.760	12.0	1.010-20	215	140	5/25/17	Albuminuric neuroretinitis	C. I. N.
			3/26/17	7.0	....	....	...	...	1.427	3.6						
			4/ 2/17	5.0	....	....	...	...	1.340	8.5						
			4/23/17	0	91.0	55.5	2.8	2.0								
			4/25/17	0	....	....	...	...	1.530	3.0						
			5/ 2/17	Trace	....	....	...	...	1.950	1.3						
			3/21/17	Trace	....	....	...	...	1.530	1.4						
119773	46	♂	3/25/16	66.7	....	....	...	...	0.445	57.5	1.010-25	150	90	5/26/17	.....	C. I. N.
			7/14/16	58.3	35.7	22.7										
			11/10/16	62.5	....	....	..	...	0.485	105.0						
			3/ 5/17	38.5	....	....	...	...	0.593	62.0						
120485	45	♂	3/30/17	20.0	....	....	...	...	0.595	12.0	1.005-15	230	135	6/10/17	Retinal hemorrhages	C. I. N.; uremia
			4/20/17	10.0	....	....	...	...	0.670	7.0						
			5/ 2/17	20.0	....	....	...	...	0.825	6.5						
			6/ 8/17	....	182.0	82.5	6.5	4.0								
121273	56	♂	1/24/17	13.3	....	....	...	...	1.190	4.5	1.010-20	205	115	7/27/17	.....	C. D. N.
			1/31/17	3.0	....	....	...	...	1.340	6.2						
			7/13/17	0	182.0	83.5	3.5	5.0								

TABLE 2.—FINDINGS IN FORTY-THREE LIVING CASES

Case No.	Age	Sex	Date of Examination	Phenolsulphonephthalein, per Cent.	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Fundus	Diagnosis
					Mg. per 100 C.c.				Gm. per L. Blood Urea			S.	D.		
					Nonprotein N	Urea N	Uric Acid	Creatinin							
107221	48	♂	7/ 1/15	40.0	55.0	29.0	...	...	.....	....	1.010-20	190	105	.....	C. D. N.
			7/21/15	50.0											
107462	36	♂	7/26/15	45.4	31.0	15.0	5.4	1.2	.....	....	1.010-20	...	...	.....	Mercurie chlorid poisoning
107516	58	♀	7/ 8/15	25.0	....	....	...	...	.....	....	1.010-20	150	95	Retinitis	C. I. N.
			8/18/15	21.3	100.0	41.5	3.7	3.7							
			8/23/15	15.0	50.0	27.5	2.7	2.0							
			8/28/15	11.0	55.0	25.0	3.4	1.0							
107859	38	♀	8/ 6/15	30.0	22.0	12.0	...	...	.....	....	.....	250	160	Retinitis	C. I. N.
			8/18/15	27.5	55.0	19.5	3.5	1.4							
			8/23/15	45.5	33.0	12.0	4.5	2.0							
			8/27/15	22.5	23.0	16.5	4.1	0.7							
			9/ 2/15	45.6	45.0	20.8	2.4	0.65							
108557	66	♂	9/15/15	15.7	125.0	91.0	...	...	.....	....	1.010	160	90	.....	C. I. N.
109620	56	♀	11/ 9/15	11.1	33.0	16.5	...	...	.....	....	1.010-20	300	200	Negative	C. I. N.
109861	65	♀	8/ 5/15	35.0	38.0	16.6	...	...	.....	....	1.015-20	180	110	.....	C. I. N.
110786	35	♀	1/10/16	Trace	170.0	125.0	...	...	.....	....	1.005-45	220	130	Hemorrhage	C. I. N.
			1/24/16	Trace	129.0	100.0									
			1/31/16	Trace	100.0	62.5									
			2/ 7/16	Trace	100.0	55.6									
			2/11/16	0	100.0	62.5									
			2/14/16	Trace	85.0	41.8	...	...	0.895	1.6					
			2/16/16	....	....	....	...	...	1.187	1.2					
			2/18/16	....	....	....	...	...	0.706	6.7					
			2/21/16	....	62.5	41.7	...	...	0.884	1.8					
			2/23/16	2.4	....	....	...	...	0.764	4.4					
			2/25/16	....	83.0	41.7	...	...	0.884	2.1					
			2/28/16	....	62.5	38.5	...	...	0.824	3.0					
			3/ 3/16	....	71.5	29.8									
			3/10/16	....	....	....	...	...	0.763	3.7					
			3/15/16	....	....	....	...	...	2.140	0.5					
			3/17/16	0.9	....	....	...	...	1.530	1.4					
			3/20/16	....	....	....	...	...	1.776	1.3					
			3/23/16	....	....	....	...	...	1.776	0.8					
			3/25/16	3.0	....	....	...	...	1.776	0.7					
			4/ 5/16	....	....	....	...	...	1.776	1.0					
112068	58	♀	3/16/16	50.0	25.0	12.3	...	...	.....	....	1.010-30	200	116	.. ..	C. I. N.
			4/ 3/16	....	28.0	14.0									
			4/ 5/16	....	....	....	...	...	0.208	92.0					
			7/ 3/16	7.7	....	....	...	...	0.535	67.0					
			10/ 4/16	57.1	...	....	...	...	0.324	76.0					

112256	42	♂	3/27/16	....	35.0	20.7	...	...	.....	....	1.015	225	150	.....	C. I. N.
112259	42	♂	3/27/16	....	50.0	24.6	...	...	.....	....	1.010-25	195	140	.....	C. I. N.
			3/31/16	....	71.5	41.5									
			4/ 3/16	46.4	62.5	35.7									
			4/ 7/16	47.2	....	....	...	...	0.710	12.0					
			4/14/16	37.1	....	....	...	...	0.535	9.0					
			4/19/16	31.2	....	....	...	...	0.595	16.0					
			4/24/16	45.0	....	....	...	...	0.763	4.5					
			5/ 1/16	30.0	....	....	...	...	0.877	10.4					
			5/ 8/16	35.7	62.5	36.0	...	...	0.667	20.0					
			5/15/16	16.7	....	....	...	...	0.764	10.0					
			5/24/16	25.0	....	....	...	...	0.892	4.7					
			5/31/16	30.0	....	....	...	...	1.070	5.0					
			6/ 7/16	28.5	....	....	...	...	0.800	9.5					
			6/21/16	....	71.5	41.7									
			6/28/16	30.0	55.5	35.7									
			7/26/16	....	....	....	...	...	0.668	9.0					
112314	22	♀	3/29/16	....	....	....	...	...	0.357	49.0	1.005-20	150	105	Negative	C. I. N.
			4/ 5/16	....	....	....	...	...	0.410	47.0					
			4/10/16	71.4	....	....	...	...	0.295	56.5					
			4/19/16	74.3	....	....	...	...	0.362	77.0					
112419	44	♀	4/14/16	....	....	....	...	...	0.280	43.5	1.020-30	160	95	.....	C. I. N.
112557	58	♀	5/24/16	10.0	....	....	...	...	0.432	33.0	1.010-30	180	100	.....	C. I. N.
			5/31/16	62.5	....	16.7									
			12/ 7/16	72.7	....	....	...	...	0.410	22.0					
113128	55	♂	5/12/16	15.3	50.0	35.5	7.1	2.0	.....	....	1.010-20	...	...	Retinitis	C. I. N.
			5/22/16	....	48.6	31.2	5.5	2.0							
			6/ 9/16	....	43.5	25.0	3.8								
			6/28/16	....	53.5	31.2	2.6								
			7/26/16	....	41.7	31.2	...	1.2							
			8/31/16	....	62.5	45.4	7.7	1.2							
			9/21/16	....	43.5	....	3.3	0.6							
113496	44	♀	5/29/16	12.5	....	....	...	...	0.347	14.0	1.005-30	...	...	.....	C. I. N.
			6/ 7/16	24.0	....	....	...	...	0.300	120.0					
113671	44	♂	6/ 7/16	50.8	....	....	...	...	0.381	9.0	1.015-20	...	...	.....	C. I. N.; alcoholic cirrhosis, liver
114162	68	♀	6/28/16	35.7	60.0	31.2	...	...	.....	....	1.010-20	100	140	.....	C. I. N.
114170	42	♂	10/20/15	95.0	21.6	9.5	...	...	.....	....	1.010-20	150	100	Thickened arteries	C. I. N.
			7/ 3/16	65.0	....	....	...	...	0.593	26.0					
114237	28	♂	7/10/16	12.2	....	....	...	...	0.445	120.0	1.010-35	140	75	.....	C. I. N.
114352	34	♀	2/14/17	8.5	....	....	...	...	0.610	8.5	1.010	140	75	.....	C. I. N.
114478	31	♂	7/21/16	8.7	....	....	...	...	.....	....	1.010-30	...	...	.....	C. I. N.
			7/28/16	7.0											

TABLE 2.—Findings in Forty-Three Living Cases—(*Continued*)

Case No.	Age	Sex	Date of Examination	Phenolsulphonephthalein, per Cent.	Blood Analysis					Urea Index	Urine, Specific Gravity	Blood Pressure		Fundus	Diagnosis
					Mg. per 100 C.c.				Gm. per L. Blood Urea			S.	D.		
					Nonprotein N	Urea N	Uric Acid	Creatinin							
115061	43	♀	10/ 1/15	50.0	36.5	16.0	5.08	...	.....	....	1.005-30	120	80	.....	A. P. N.
			10/ 6/15	50.0	20.0	11.0	1.65								
			10/27/15	55.6	21.0										
			12/ 1/15	66.7	18.0	7.2	1.25								
			8/23/16	68.6	25.0	14.7	...	...	0.315	39.5					
115106	49	♂	8/25/16	66.7	....	....	...	...	0.382	45.0	.....	...	...	.....	C. I. N.
			1/ 3/17	....	....	....	...	...	0.412	85.0					
			5/ 7/17	....	....	....	...	...	0.268	79.0					
115570	46	♀	6/23/16	25.0	....	....	...	...	0.411	27.0	1.005-20	228	150	Retinitis	C. I. N.
			9/22/16	10.0	....	....	....	...	0.900	1.22					
115657	57	♀	10/ 2/16	14.4	....	....	...	...	0.713	12.5	.....	230	120	Negative	C. I. N.
			1/31/17	28.7	....	....	...	...	0.668	17.0					
			3/ 7/17	....	71.5	38.5									
115875	69	♂	7/ 3/16	12.8	....	....	...	...	0.535	14.0	1.005-25	170	90	.....	C. D. N.
			10/14/16	31.5	....	....	...	...	0.535	25.0					
115945	52	♀	10/14/16	70.0	....	....	...	...	0.824	10.7	1 020-25	240	140	Hemorrhages	C. I. N.
116896	8	♂	10/ 5/15	63.0	....	....	...	...	.....	....	1.010-30	...	...	.....	C. I. N.
			10/20/15	80.0	50.0	....	3.2								
			10/30/15	10.0											
			11/ 5/15	71.4											
			11/23/15	74.3											
			12/ 7/15	23.6											
			12/23/15	86.7											
			2/ 9/16	83.3											
			3/14/16	....	38.5	24.7	2.75								
117170	57	♂	12/27/16	71.4	....	....	...	...	0.255	19.4	1.010-25	230	220	.....	C. I. N.
117230	41	♀	12/21/16	31.6	....	....	...	...	0.199	74.0	.....	210	180	Old hemorrhage	C. I. N.
			12/29/16	71.4											
117504	69	♂	1/17/17	62.5	....	....	...	...	0.445	37.0	1.005-20	175	120	.....	C. N.
			1/31/17	21.0	....	....	...	...	0.314	21.0					
			2/ 7/17	28.0	....	....	...	...	0.368	24.0					
117628	49	♂	12/ 9/16	29.0	....	....	...	...	0.428	24.0	1.010-15	200	110	.....	C. I. N.
			1/25/17	25.0	....	....	...	...	0.485	27.0					
118397	30	♀	2/21/17	27.3	....	....	...	...	0.255	20.0	1.010-25	130	85	Negative	C. I. N.
			2/28/17	51.2	....	....	...	...	0.428	33.0					
			3/17/17	70.0	....	....	...	...	0.382	34.0					
			3/14/17	50.0	....	....	...	...	0.267	153.0					

118449	66	♀	2/28/17	5.6	....	....	...	...	0.829	4.0	1.010-25	200	105	.....	C. I. N.
			3/ 7/17	10.0	....	....	...	...	1.190	6.0					
			3/30/17	10.0	....	....	...	...	0.975	6.0					
118461	14	♂	2/24/17	62.5	....	....	...	...	0.593	62.0	1.005-20	130	70	.....	C. I. N.
			3/ 5/17	22.7	....	....	...	...	0.334	44.0					
			3/14/17	71.4	....	....	...	...	0.267	100.0					
118523	59	♂	2/ 9/17	22.2	....	....	...	...	0.485		.....	...	...	.....	C. I. N.
			2/28/17	26.3	....	....	...	...	0.344	36.0					
			3/ 9/17	40.0	....	....	...	...	0.445	42.0					
			3/28/17	38.5	....	....	...	...	0.356	33.0					
118726	71	♂	6/ 7/16	27.8	....	....	...	...	0.892	2.5	1.010-20	220	100	.....	C. I. N.
			6/21/16	50.0	....	....	...	...	0.300	29.0					
118754	65	♀	3/14/17	22.2	....	....	...	...	0.710	6.0	1.010-20	180	110	.....	C. I. N.
118782	14	♂	3/14/17	85.0	....	....	...	...	0.535	42.0	1.010-20	175	100	.....	Acute N.
			3/30/17	42.9	....	....	...	...	0.486	72.0					
119340	28	♂	4/13/17	26.7	....	....	...	...	0.357	76.0	1.010-20	134	80	Negative	C. I. N.
			4/25/17	35.7	....	....	...	...	0.308	60.0					
			5/ 2/17	38.5	....	....	...	...	0.510	35.0					
			5/14/17	40.0	....	....	...	...	0.357	29.0					
			5/25/17	24.0	....	....	...	...	0.282	62.0					
			6/ 4/17	41.7	....	....	...	...	0.314	118.0					
			6/13/17	31.2	....	....	...	...	0.535	23.0					
			6/22/17	29.2	....	....	...	...	0.465	26.0					
120030	51	♂	3/ 9/17	21.4	....	....	...	...	0.562	48.0	1.010-20	200	100	Hemorrhages	C. I. N.
			3/14/17	....	31.5	17.8	5.5	1.0							
			3/26/17	20.0	....	....	...	...	0.357	42.0					
			5/21/17	15.0	....	....	...	...	0.665	13.8					
			5/27/17	24.7	....	....	...	...	0.535	13.0					
121060	43	♂	7/ 3/16	16.5	....	....	...	...	0.593	5.5	1.010-20	...	..	....	C. I. N.
			7/ 7/16	17.5	....	....	...	...	0.535	12.0					
			7/19/16	10.3	....	....	...	...	0.535	13.0					
			7/26/16	40.0	....	....	...	...	0.535	16.5					
			8/ 2/16	23.1	....	....	...	...	0.479	15.7					
			8/ 9/16	30.0	....	....	...	...	0.595	10.0					
			8/18/16	25.0	....	....	...	...	0.382	20.0					
			8/23/16	26.3	....	....	...	...	0.428	20.5					
			8/30/16	30.0	....	....	...	...	0.446	20.0					
			10/ 4/16	21.3	34.5	25.0	...	...	0.535	15.0					
			10/23/16	33.3	....	....	...	...	0.629	11.0					
			11/20/16	46.3	....	....	...	...	0.382	24.0					
			1/ 1/17	62.5	33.4	27.8	...	...	0.595	13.0					
			1/28/17	30.7	....	....	...	...	0.334	28.5					
			4/16/17	41.7	....	....	...	...	0.595	11.0					

STUDIES ON RENAL FUNCTION DURING AND IMMEDIATELY FOLLOWING SOME OF THE ACUTE INFECTIOUS DISEASES*

CHANNING FROTHINGHAM, M.D.
BOSTON

It is well known that definite anatomic lesions may occur in the kidney during the course of almost any of the acute infectious diseases. These lesions are usually, if not always, associated with clinical signs such as edema, scanty urine, the appearance of albumin in the urine, or abnormal findings in the sediment. The renal function as studied by various special tests is much impaired in these cases, as has been shown by Schwartz and McGill.[1] Naturally such acute lesions in the kidney often result in permanent anatomic injury to the kidney, with or without disturbance in renal function.

In other cases during acute infections it is not uncommon to find albumin and casts in the urine without any other clinical evidence of renal disturbance. Also, during the course of an acute infection, there may be a decrease of substances normally found in the urine, such as the low chlorid content of the urine in pneumonia. It is not always clear whether these variations are due to renal disturbances or not. Still other cases during the course of acute infections fail to show any evidence of renal disturbance by the usual routine examination of the urine. The question arises whether or not these cases without apparent renal involvement would show any disturbance in renal function by the special tests more recently devised for the purpose, either during the febrile period or soon after. This is of especial interest in view of the tendency at present to force feedings during the course of many of the acute infections, which presumably puts an increased load on the kidneys.

Amid the variety of tests for renal function which have received considerable attention of late years, three or four stand out as being the most satisfactory for ordinary clinical work. In this clinic at present the renal function is studied by Rowntree and Geraghty's[2] test for

* Submitted for publication March 23, 1918.

* From the Department of Medicine, Harvard University, and the Medical Clinic, Peter Bent Brigham Hospital.

* Presented at the meeting of the Association of American Physicians, May, 1917.

1. Schwartz, H., and McGill, C.: THE ARCHIVES INT. MED., 1916, **17**, 42.

2. Rowntree, L. G., and Geraghty, J. T.: Jour. Pharmacol. and Exper. Therap., 1909, **1**, 579.

the elimination of phenolsulphonephthalein in the urine after intramuscular injection, the estimation of the blood urea by the urease method of Van Slyke and Cullen,[3] and the estimation of the index of urea excretion as determined by McLean's[4] formula based on Ambard's laws. In addition, the renal function is investigated by studying the output and concentration of the urine and also of the sodium chlorid and nitrogen in the urine, collected at two-hour intervals during a day in which the patient is on Christian's[5] modification of the renal test diet devised by Hedinger[6] and Schlayer.

Although the last mentioned test is probably more comprehensive than the others, it is not so well adapted for acute infections, in which the patients often can not eat the required diet and find difficulty in voiding urine every two hours. Studies on renal function by means of some one or more of these tests during the course of acute infections have been reported by a few observers. Thus Tileston and Comfort,[7] in 1914, reported on the urea in the blood in various acute processes. They found the nonprotein nitrogen and urea of the blood elevated, in cases of pneumonia during the fever, but not elevated in typhoid fever, acute rheumatism and uncomplicated scarlatina. Schwartz and McGill,[1] in 1916, reported an increase in the blood urea and diminution of phenolsulphonephthalein excretion in many cases of pneumonia and some other febrile conditions. In epidemic meningitis they found no changes in these tests for renal function. They did not separate carefully, however, the cases that showed evidence of acute nephritis from those that did not.

In this work the renal function of cases during and just after an acute infection was studied by the phenolsulphonephthalein test,[2] the estimation of blood urea,[3] and the determination of McLean's[4] index of urea excretion. In addition, evidence of renal irritation was sought for by examination of the urine for albumin, red blood cells and casts. Usually all the tests were performed on the same day. Occasionally the phenolsulphonephthalein test or the urine examination was done on the day following the urea determinations. Cases were selected among young people who presented no evidence of chronic nephritis and no evidence of acute nephritis as sought for by the usual urinary studies. The results have been grouped by diseases and recorded in tables with an accompanying discussion of the findings.

---

3. Van Slyke, D. D., and Cullen, G. E.: Jour. Biol. Chem., 1914, **19,** 211.
4. McLean, F. C.: Jour. Am. Med. Assn., 1916, **66,** 415.
5. O'Hare, J. P.: The Archives Int. Med., 1916, **17,** 711.
6. Hedinger, M., and Schlayer: Deutsch. Arch. f. klin. Med., 1910-1911, **114,** 120.
7. Tileston, W., and Comfort, C. W., Jr.: The Archives Int. Med., 1914, **14,** 620.

Technic.—The phenolsulphonephthalein was injected intramuscularly as originally described by Rowntree and Geraghty and the urine collected after the first and second hour. The total for the two hours is recorded. This test and the examination of the urine were made for me by the house staff of the hospital, and to them I am indebted. At this hospital an excretion in two hours of 50 per cent. of the phenolsulphonephthalein injected is considered normal. In estimating the index of nitrogen excretion the urine was collected over a period of two hours between 8 and 10 a. m. One-half hour before this the patient was given about 200 c.c. of water. At 9 a. m. the blood was collected from a vein and prevented from clotting by oxalate crystals. The urea nitrogen was determined in the blood and urine by means of the urease method described by Van Slyke and Cullen.[3] In this hospital the blood urea nitrogen is considered normal when it falls between 10 and 20 mg. per 100 c.c. of blood. The ammonia in the urine was determined according to the method used by the same authors. In a few of the cases in which the urine could not be collected exactly at the end of two hours, it was collected as soon after as possible and proper allowances made in estimating the twenty-four-hour quantity. Just what should be considered a normal index of urea excretion is difficult to decide, but the normal probably falls between 70 and 170 per cent.

TABLE 1.—TYPHOID FEVER

Hosp. No.	Age	Date	Temp.	Blood Urea, Mg. per 100 C.c.	C	D	Index per Cent.	Phthal. per Cent. 2 Hrs.	Urine		
									Alb.	Casts	R.B.C.
5088	13	12/ 2/16	101.5	10.25	13.4	20.1	267	66	0	0	0
		12/19/16	Normal	11.18	13.6	15.5	170	60	0	0	0
5311	26	10/ 3/16	103.5	14.9	31.8	36.71	294	..	VSTr.	0	0
		12/ 9/16	Normal	8.39	3.02	11.02	126	40	0	0	0
5487	18	10/27/16	103.0	11.42	25.6	15.36	272	52	SPTr.	0	0
		11/18/16	Normal	10.95	2.68	8.95	58	75	0	0	0
5337	15	10/ 3/16	103.4	6.5	5.01	13.73	287	..	VSTr.	0	0
		11/ 4/16	Normal	7.9	6.18	4.38	72	..	SPTr.	0	0
5738	20	12/12/16	101.0	8.6	20.82	29.15	530	45	0	0	0
		12/21/16	Normal	12.78	6.48	20.22	106	67	SPTr.	0	0
5568	27	11/11/16	101.0	6.9	6.7	6.27	135	58	Trace	0	0
		12/ 9/16	Normal	8.2	4.66	12.58	184	70	0	0	0

In Table 1 are recorded the studies on six cases of typhoid fever. There was no reason to suspect any disturbance of the kidneys in these cases and the examination of the urine showed no evidence of renal irritation except for traces of albumin in some of the cases. The second set of studies for renal function in these cases was not made until the temperature had been normal for a week or more. In those cases in which the elimination of phenolsulphonephthalein was studied it is seen that in three of the four cases it was lower during the fever than after, yet all the readings were within what we call normal limits. In the other case the phenolsulphonephthalein output was higher during the fever than after. The blood urea remained within normal limits both during and after the fever. In some cases it was slightly higher during the febrile period than after, but this variation was not consistent, for in other cases the blood urea was lower during the fever than

after. All of these patients were on a high caloric diet, which they were taking well during the course of the fever. The index of urea excretion, on the other hand, in five of the six cases during the fever, was considerably elevated above the normal and above what it was in the same case after the temperature had fallen. The indexes of excretion when the temperature was normal fell within the rather wide limits allowed for normal, although some were at the lower end and others at the upper edge of the limits. The sixth case showed practically normal indexes during and after the fever, with the index somewhat higher after the temperature was normal. This was apparently as typical a case of typhoid as the other and no reason for the variation from the other cases was suggested.

In these tables the amount of urea estimated for the twenty-four hours, called "D," and the concentration of the urea in the urine, called "C," are also included. The cause for these high indexes during fever is apparently not due to constant variations in any one of the factors

TABLE 2.—PNEUMONIA, TYPE I

Hosp. No.	Age	Date	Temp.	Blood Urea, Mg. per 100 C.c.	C	D	Index per Cent.	Phthal. per Cent. 2 Hrs.	Urine		
									Alb.	Casts	R.B.C.
5720	28	12/ 7/16	103.0	10.25	12.72	22.9	270	83	Sl. tr.	Many	0
		12/19/16	Normal	12.58	9.2	17.88	150	55	0	0	0
6095	42	2/ 8/17	100.0	36.12	31.5	32.4	43	52	Sl. tr.	Many	0
		2/20/17	Normal	16.6	23.32	22.38	127	..	0	0	0
5930	25	1/11/16	102.5	29.6	26.64	27.07	59	60	Trace	Few	0
		1/18/16	Normal	14.9	20.27	21.89	169	55	0	0	0
5907	39	11/ 9/16	103.0	16.3	34.6	19.03	183	55	Sl. tr.	Few	0

used in its estimation, so that one is unable to say that the high index was due to a constantly low blood urea, or high concentration of the urea in the urine, or increased total quantity of urea. The main feature is that most of these cases put out either a larger amount of urea during fever than after or else in a considerably more concentrated form in proportion to its concentration in the blood.

In Table 2 are recorded four cases of pneumonia which were classified in Group 1 of Cole's[8] classification for pneumococci. These four cases showed evidence of renal irritation by the presence of albumin and casts in the urine during the fever. In the two cases in which the phenolsulphonephthalein test was studied during and after the fever, it showed a better excretion during the fever than after and was quite elevated in one of the cases. In the other two cases in which the phenol-

8. Cole's Classification. Dochez, A. R., and Gillespie, L. J.: Jour. Am. Med. Assn., 1913, **61**, 727.

sulphonephthalein excretion was studied only during the fever, the output was also normal. Two of the cases showed an elevated blood urea nitrogen during the fever. One of these had been given the specific antipneumococcus serum the night before; the other had not. The index of urea excretion in two of these cases was low during the fever and returned to normal after. In one of the other cases in which the blood urea was normal the index was elevated during the fever and returned to normal in convalescence. In the fourth case the blood urea was normal and the index was at the upper end of normal limits during the fever. This patient (5567) developed an empyema and subsequent study in the afebrile period was not done. In the two cases with the low index during the fever the output and concentration of the urea in the urine was quite high, but not enough so in proportion to the blood urea to keep the index normal. There was no constant variation in the relation of "C," "D" and the blood urea in the cases with the high indexes.

TABLE 3.—Pneumonia, Type IV

Hosp. No.	Age	Date	Temp.	Blood Urea, Mg. per 100 C.c.	C	D	Index per Cent.	Phthal. per Cent. 2 Hrs.	Urine		
									Alb.	Casts	R.B.C.
5553	33	11/ 7/16	104.0	8.16	4.24	15.77	221	50	Sl. tr.	Rare	0
		11/18/16	Normal	11.18	5.63	10.13	86	70	SPTr.	0	0
5829	38	12/27/16	104.0	12.68	18.66	32.02	268	..	SPTr.	0	0
		1/11/17	Normal	15.84	10.9	20.27	104	..	0	0	0
5940	15	1/13/17	103.0	12.68	19.35	56.89	640	70	VSTr.	Many	0
		1/30/17	Normal	20.7	13.33	15.2	54	45	0	0	0
5946	20	1/13/17	101.0	25.96	47.25	42.6	135	55	Trace	Num.	0
		2/ 1/17	Normal	17.7	8.17	17.3	53	50	0	0	0
6205	23	2/27/17	100.5	13.37	22.4	9.44	96	55	SPTr.	0	0
		3/ 6/17	Normal	14.45	16.18	16.12	116	59	SPTr.	0	Many
5817	45	12/23/16 Died	102.0	22.83	17.98	32.36	105	45	VSTr.	0	0

In Table 3 are recorded six cases of pneumonia which belong to Group IV of Cole's classification. Several of these cases show evidence of renal irritation during the febrile period, as evidenced by the presence of albumin and casts in the urine. In these cases during and after the fever, the phenolsulphonephthalein elimination was within normal limits except in two instances, when it was only just below the normal. In two of these cases there was considerable variation in the phenolsulphonephthalein elimination during the febrile period from that after the fever had subsided. In one of the cases (5553), however, the elimination was more after the fever, in the other (5940) the excretion was more during the fever. The blood urea was slightly elevated during the fever in two of the cases. In these two cases, however, the index of urea excretion was normal. In three other of these six cases, however, during the fever the index of urea excretion was elevated,

and in one of them markedly so. In the five cases which recovered, the indexes of urea excretion were normal after the fever except in two. These two showed a moderate diminution of the index down nearly to 50 per cent. It is interesting to note that in one of these cases the index had been exceptionally high during the fever, and this suggests the possibility of fatigue appearing after the excessive activity. In the one case in which the patient died, the index of excretion was normal during the fever. The relations between "C," "D" and the blood urea do not show any constant variations to account for the variation in the indices.

In Table 4 are recorded five cases of acute articular rheumatism, in three of which (6203, 6256 and 6222) acute joint symptoms were present. In the other two (5774 and 6381) the joint symptoms had subsided a few days before and the fever was due to cardiac complications. The evidence of renal irritation, from an examination of the urine in all of these cases, did not exist except for possibly very slight

TABLE 4.—ACUTE ARTICULAR RHEUMATISM

Hosp. No.	Age	Date	Temp.	Blood Urea, Mg. per 100 C.c.	C	D	Index per Cent.	Phthal. per Cent. 2 Hrs.	Urine		
									Alb.	Casts	R.B.C.
6203	24	2/27/17	101.0	19.34	15.74	26.39	76	50	VSTr.	0	0
		3/ 8/17	Normal	17.71	10.83	11.17	33	40			
6256	28	3/ 8/17	100.0	18.17	23.6	31.72	162	..	0	0	0
		3/15/17	Normal	20.22	17.53	27.78	98	52	0	0	0
6222	32	3/ 1/17	100.0	16.31	29.32	31.66	192	54	VSTr.	Occ.	0
		3/22/17	Normal	17.7	19.3	29.60	139	44	0	0	0
5774	13	12/30/16	100.5	15.47	46.31	29.41	357	35	SPTr.	0	0
		1/25/17	Normal to 99.0	9.32	5.05	11.8	129	50	0	0	0
6381	16	4/ 5/17	100.0	15.38	40.1	38.0	427	67	VSTr.	Rare	0
		5/ 4/17	Normal	9.7	13.46	18.1	305	72	0	0	0

irritation in Cases 6222 and 6381. In only one of these cases was the phenolsulphonephthalein output below normal during the fever. In two others it was below normal after the temperature had returned to normal. In all the cases the blood urea nitrogen was practically normal during and after the fever without any consistent variation between the two periods. In one of these cases the index of urea excretion was at the lower limits of normal during the fever, but this same case showed the index still lower after the fever. In the four other cases the index during the febrile period was toward the upper limits of normal in the two without symptoms and considerably elevated in the two with cardiac complications. In one of the cases with cardiac symptoms the index remained considerably elevated after the temperature was normal. In the other cases it became normal after the fever except in the one case already mentioned, in which it fell below

normal. As in the other group, there are no consistent variations in the "C" or "D" or the blood urea content to account for variation in the index.

In Table 5 are grouped together a few cases of acute infection of various sorts. Although in two of these cases (6247 and 6009) there was some evidence of renal involvement, they were included for comparison. In the diphtheria case the interesting points to be noted are the increased index of urea excretion during the fever and the slight diminution of phenolsulphonephthalein excretion after the temperature had reached normal. Otherwise the tests were normal.

In the case of gonorrheal arthritis, the index of urea excretion was considerably increased during the febrile period and in the second test

TABLE 5.—MISCELLANEOUS

Hosp. No.	Age	Date	Temp.	Blood Urea. Mg. per 100 C.c.	C	D	Index per Cent.	Phthal. per Cent. 2 Hrs.	Urine			Comments
									Alb.	Casts	R.B.C.	
5630	20	11/21/16	99.5	16.2	29.23	43.85	297	65	VSTr.	0	0	Diphtheria; serum given 11/20/16
		12/ 5/16	Normal	12.58	4.3	20.38	97	40	0	0	0	
5687	23	12/12/16	99-101	9.55	24.52	36.78	500	67	0	0	0	Gonorrheal arthritis
		12/23/16	Nor.-100	10.95	13.0	32.4	274	58	0	0	0	
5888	30	1/ 6/17	103.5	12.16	21.4	29.5	254	..	0	0	0	Abscess periosteum
		2/ 1/17	Normal	16.96	2.5	14.1	24	..	0	0	0	
6151	43	2/17/17	100.0	24.7	30.28	30.88	44	50	0	0	0	Acute gout; obese
		3/ 1/17	Normal	16.54	13.72	16.46	36	21	0	Rare	0	
6247	19	3/ 6/17	102.0	21.44	14.36	8.96	21	41	Trace	0	Some	Cervical adenitis following tonsillitis
6247	..	3/10/17	Normal	13.42	12.9	11.61	69	40	VSTr.	0	0	Acute nephritis
6009	26	1/23/17	102.0	54.5	16.5	23.43	9	0	VSTr.	0	Few	Bronchopneumonia
		2/13/17	Normal	16.35	3.55	16.61	41	50	0	Many	0	Acute nephritis

it was still quite elevated. It is only fair to say, however, that at this time the temperature still showed a slight afternoon elevation at times.

The index of urea excretion during the febrile period in the case which showed an abscess of the periosteum was quite elevated, and after the fever was unusually low. Unfortunately in this case the phenolsulphonephthalein elimination was not completed.

In the patient with acute gout and obesity, although the phenolsulphonephthalein elimination was normal during the fever, it became lowered considerably after the febrile period. The index of urea excretion was below the normal in both examinations.

The case of cervical adenitis which from the urine examination and clinical picture suggested some renal involvement, showed a phenolsulphonephthalein excretion which was persistently slightly below normal during the fever and after. The index of urea excretion also was considerably lowered during the fever but returned practically to normal after the fever.

In the case of severe bronchopneumonia with clinical evidence of renal involvement, the phenolsulphonephthalein elimination was nothing and the index of urea excretion was very low. In convalescence the phenolsulphonephthalein elimination returned to normal but the index of urea excretion only returned toward normal, still remaining lowered. In this case during the febrile period the blood urea was considerably increased in amount.

These last two cases are of interest in that they show that any renal involvement which tends to disturb the functional tests more than offsets any tendency for the index of urea excretion to be elevated, as has been noted to occur in many instances during the febrile period.

It is evident from glancing at these tables that in the cases of acute infection in which there is no evidence of serious renal involvement, there is no constant impairment of renal function, as shown by these tests, either during or after the acute stage of the infection has passed. In some of the cases in the various diseases certain suggestions of impairment of function occur but not consistently enough to draw any definite conclusions. Thus, in the group of pneumonia cases of Type I the blood urea was elevated in two cases during the fever and the index of excretion lowered in these cases. In one case of pneumonia Type IV, the renal function was slightly below the average in two of the tests after the fever in a case in which the function had been especially active during the fever. Also, in one of the cases of rheumatic fever the function as shown by the index and phenolsulphonephthalein was below normal after the fever. In this case there had been no increase in function during the fever. On the other hand, the striking feature about many of these cases in all the groups was the frequency of an abnormally high index of urea excretion during the course of the fever. As this increase in the index was not associated with an increase in the phenolsulphonephthalein excretion or an abnormally low blood urea, in most of these cases it seems more likely that it depends on some factors peculiar to fever which affect this test rather than to a hyperactivity of the kidneys during fever. Just what the factors are which caused this high index are not made clear by this study.

From these studies it may be concluded that these tests for renal function, namely, the phenolsulphonephthalein elimination, the urea nitrogen in the blood, and the index of urea elimination, failed to show consistent evidence of impaired renal function during the course of or following these acute infections in which the clinical picture or the urinary examination by the older methods showed nothing suggestive of acute nephritis.

Peter Bent Brigham Hospital.

ALKAPTONURIA

S. S. SCHOCHET, M.D.
CHICAGO

The occurrence of alkaptonuria is sufficiently rare to justify the publication of the following case. Only nine of the seventy or so recorded cases of alkaptonuria have been reported occurring in the states.

As the exact cause of this condition is still unknown and as relatively few cases have been reported, it seemed well to add this record to those which have been published, with the findings and result of treatment. Fromherz has recently expressed the opinion that many alkaptonurics remained unnoticed, and he calls attention to the fact that forty-five of the seventy cases have been reported within the last fifteen years.

The term alkaptone (from *alkali* and κάπτειν, "to absorb greedily") was first ascribed by Bödeker in 1857 to a substance found in the urine of a patient, which possessed two chief characteristics: first, the power to reduce alkaline copper solutions, and secondly, the property of absorbing oxygen from the atmosphere in the presence of alkali, and as a result turning to a brown-black color.

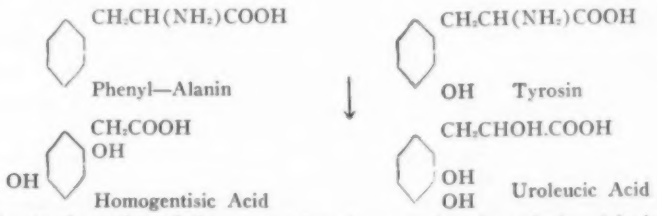
The urine may be clear and of normal color when passed, but later becomes of a dark brown and finally black color on exposure to the air. This condition may be present in cases of ochronosis, but is not a necessary accompaniment of this affection. Gouget has found a number of references in the literature of the past to cases of melanuria which were probably instances of alkaptonuria. Thus, Scribonius (1584), Zacutus and Lusitances (1649) describe cases of young children in apparent health who passed black urine; and Scheneck (1609) reports the case of a Monk who presented the same urinary anomaly during his whole life.

In 1875 Ebstein and Müller obtained a substance from the urine of an alkaptonuric patient by treating the urine with alcohol-ether, which formed the reactions given by pyrocatechin. This observation was of interest because it was the first case in which the opinion had been expressed as to what the reactions in alkaptonuria were. Fleischer next observed a urine which gave similar reactions with those of Fürbinger in which he was able to demonstrate small quantities of pyrocatechin. Bödeker in a communication to Fürbinger expresses the view that his alkaptone bodies might be similar to pyrocatechin.

* Submitted for publication April 9, 1918.

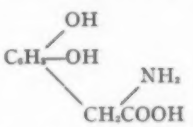
About this date Baumann reported that pyrocatechin is a normal constituent of horses' urine, and that frequently, if not regularly, is present in varying amounts in human urine.

An excess of excretion of the normal constituent of pyrocatechin in the urine led many to the belief that it was identical with alkaptonuria. This view was expressed by Salkowski and Leube, who said: "Apparently identical with pyrocatechin is the alkaptone of Bödeker and Furbinger." The opinion has been expressed of late that homogentisic acid (hydroquinon-acetic acid), which is apparently derived from tyrosin, is a normal intermediary product in the destruction of tyrosin and phenylalanin, that its formation represents an oxidation which precedes the breaking up of the benzene ring, and that its appearance in the urine is an expression of metabolic insufficiency which renders the destruction of the benzene ring impossible..



Due to the action of the enzyme tyrosinase on tyrosin and phenylalanin

In 1886 and 1889 Kirk made a further contribution to our knowledge regarding alkaptonuria. The report is of interest chiefly because it is the first instance recorded in which the urine of more than one member of a family presented the characteristics of alkaptonuria. The opinion was conveyed that the condition may be congenital and occur in the offspring of consanguineous marriages. To Baumann and Wolkow we are indebted for the most exhaustive study of the subject of alkaptonuria. They were able to obtain the "alkaptone" in pure form, to ascertain its constitution, and to determine its derivation as a product of tissue metabolism. From the urine they isolated in pure form homogentisic acid, which has the following formula.



It crystalizes in the form of large, transparent, prismatic crystals, which melt at 146.5 to 147 C. and become yellow when free from water. They are not hygroscopic, and are soluble in water, ether, chloroform, benzene and in toluol. The authors draw comparisons

between homogentisic acid and the glycosuric acid of Marshall and the urolencinic acid of Kirk, showing the marked similarity in constitution.

Embden studied another case of alkaptonuria and concludes as a result of his work, first, that we know nothing definite as to the etiology or place of formation of the homogentisic acid, and secondly, that the evidence that homogentisic acid is derived from tyrosin in the intestine as a result of the action of micro-organisms is rather against than for this view.

As to treatment, there is nothing to be done, as the condition is of no pathologic significance. Alkaptonuria is of importance, however, owing to the liability of its being mistaken for glycosuria. The negative results with bismuth ferrocyanid and the polariscopic tests should at once rule out glycosuria.

REPORT OF CASE

History.—The case here recorded occurred in a male patient, aged 32, married, the father of two healthy children (the urine of these were normal). There was no history of alkaptonuria in the family. The patient was a civil engineer, but was employed as a chemist for the previous two years.

Present Illness.—Complained of passing black urine, with periodic attacks of urticaria.

Previous Illness.—Had herpes zoster fifteen years prior to this consultation. He denied all genito-urinary infection.

Examination.—The patient was a well developed, muscular, white man, height, 5 feet 8 inches; weight, 162 pounds.

Eyes: Reflexes normal; ophthalmoscopic examination negative; no abnormal pigmentation of retina.

Heart and chest and abdomen were normal.

The physical findings were negative except for the passage of a brown-black urine.

The Wassermann reaction before treatment was negative; after administration of large doses of potassium iodid (40 to 60 grains three times a day) there was a four plus reaction.

The Urine: Physical Properties.—Appearance: When fresh, the urine was a light brown color, at times clear and free from sediment.

Color: On standing the urine perceptibly darkened, and this change was the more pronounced the longer the urine was exposed to the air, until it became of an inky black color. Fleischer says it is at first, almost black; later brown by reflected light. This condition was not determined.

Odor: There was a peculiar and slightly aromatic odor when freshly voided.

Volume: From the statements of other writers many alkaptonurics excrete either an excessive or deficient quantity of urine. Some of the patients had other maladies; for this reason, perhaps, these divergencies from the normal are of no particular significance as far as alkaptonuria is concerned. In the following instances the quantity of urine was less than 1,000 c.c.: Fürbringer's case, quantity small; average 600 c.c.; Brunne's, 900 c.c.; Ogden's, 974 c.c., and Moraczewski's, 500 to 1,200 c.c., and later 200 to 400 c.c.; Stier's, 360 to 1,030 c.c.; Hirsch's 700 c.c.; Garrod's, scanty and highly concentrated. On the other hand, the following observers have reported quantities exceeding 2,000 c.c., namely, Garner and Voirin, 2,000 to 4,000 c.c.; Stange, 1,000 to 4,000 c.c. However, more instances of deficient than excessive quantities seem to have been recorded. In my case 1,400 c.c. was the average.

Specific Gravity: The specific gravity of alkaptonuric urine in several instances appears to have been high. Urines ranging from 1.020 to 1.025 have been recorded by Fürbringer, Armstrong, Smith, Brune, Noccioli and Donsencci and Hammarstein and Schumm. In my case there was a specific gravity of 1.021.

Chemical Properties.—Acidity: I did not attempt to determine the acidity of the urine quantitatively, but merely tested each sample with litmus paper and found it to be decidedly acid. Alkaptonuric urine seems to retain its acidity for a considerable time on standing.

Fermentation, sugar, albumin, blood and blood pigments were absent.

Copper Tests: Alkaptonuric urine will reduce Fehling's solution only on being heated, but to no extent with a cold solution. Supernated alkali solution on the urine produced a black zone but no precipitate (sodium hydroxid 10 per cent.).

Spectroscopic examination was negative for bands due to iron.

Clinical Analysis.—Alkaptonuria must be differentiated from the hemoglobinurias due to drugs (phenols) and diseases (malaria, etc.) by the presence of hemoglobin in the urine; from the melanurias and hematoporphyrinurias, and especially from the condition known as "paroxysmal hemoglobinuria frigore," by chemical and spectroscopic tests for the pigments.

As no treatment has been indicated in the various textbooks, at the suggestion of Dr. Schultz I attempted to unite the benzene ring of alkaptone with the benzoates, but with negative results. After continued failure to relieve the patient of his black urine, and in spite of a negative Wassermann I administered large doses of potassium iodid (from 40 to 80 grains, increasing to 100 grains three times a day). At the end of three days the patient had a severe iodid rash, and at the end of two weeks' treatment (modified) the urine became normal in physical appearance and in its chemical composition. Another blood test was made which showed a strongly positive Wassermann (4+). I doubted the specificity and accuracy of the test and two specimens of blood were submitted to Dr. Benjamin Gruskin of the Medical Research Laboratory and to Dr. Fischer. Reports of four plus Wassermann were returned for each specimen. I then administered 10 grains of tyrosin and twenty-four hours later submitted new specimens. The reports from these two laboratories and my own test showed a negative Wassermann. Therefore, the patient twenty-four hours after the administration of 10 grains of tyrosin turned a fully four plus Wassermann reaction into a fully negative one.

In a hasty review of the literature on the Wassermann reaction I found a somewhat similar condition reported by Söderbergh in which a strongly positive Wassermann reaction was converted by the administration of sodium bicarbonate and tyrosin into a negative test.

A further note on this phase will be published in a separate communication.

I had delayed the report of this case until the present time in the hope that a more complete study could be made, but in view of the fact that I am on active service with the colors in France and no opportunity for continued work along this line is possible at present, I wish to make this preliminary report.

I beg to acknowledge my indebtedness to Dr. Solomon Strauss for confirmation of my chemical findings and to Dr. Schultz of the Michael Reese Research Institute for many helpful suggestions in this study.

OCCLUSION OF THE ENTIRE INFERIOR VENA CAVA BY HYPERNEPHROMA, WITH THROMBOSIS OF THE HEPATIC VEIN AND ITS BRANCHES*

VICTOR C. JACOBSON, M.D.,
AND
ERNEST W. GOODPASTURE, M.D.
BOSTON

Although renal hypernephroma is of relatively frequent occurrence and metastasis by way of the venous system the usual mode of dissemination of the tumor tissue, it is rare to find extensive growth into the inferior vena cava and rarer still to have an intravascular hypernephroma occlude this vessel in its entire length and extend into the right chambers of the heart.

In the present instance we have the unique picture of occlusion of the entire inferior vena cava from a hypernephroma growing along the left renal vein, completely filling the inferior vena cava from the iliac bifurcation to the right auricle, with the tumor mass extending through the tricuspid orifice into the right ventricle. The hepatic veins were thrombosed. There was acute central necrosis of the liver and death in acidosis.

REPORT OF CASE

History.—The patient, a man aged 63, entered the medical service of the Peter Bent Brigham Hospital, Jan. 22, 1917 (Med. No. 11605), complaining of swelling of the feet, legs and scrotum, shortness of breath, loss of appetite, and "gas on stomach." At that time the following history was obtained: He had been a druggist for forty years and quit work but two days previous to entrance. His appetite had been fairly good prior to the last six months, bowels were always regular and he had never had jaundice, colic, vomiting or other gastro-intestinal symptoms. Hematuria had never been noticed. His weight had suffered considerably the previous six months. In September, 1916, he weighed 184 pounds and on entrance to the hospital only 113 pounds. He said the marked loss of weight was due to his poor appetite.

After returning from his vacation in September, 1916, he noticed that his appetite was failing, and soon he began to have eructations of gas after eating. During the last three months he could not eat as much as previously because he felt "filled up" and at times, but not frequently, he regurgitated a little food. He gradually decreased the amount eaten at a meal but did not eliminate any elements of his diet. There was distress and sense of fullness in the epigastrium after meals.

Three weeks before admission he noticed for the first time that his legs and scrotum were slightly swollen, more so at night. A physician told him

* Submitted for publication March 20, 1918.

*From the Medical Clinic and Pathological Laboratory of the Peter Bent Brigham Hospital.

his urine contained a little albumin and he was warned against "kidney trouble." Digitalis, taken for two weeks, caused no improvement in the swelling. Ten days later another physician prescribed gentian and iron, with the result that his appetite increased. There was then marked shortness of breath on exertion, gradually increasing, but not sufficient to keep him from work. Three days before admission his urine was examined but no albumin was found. He was advised to enter the hospital to rest up.

Physical Examination.—At entrance this showed the patient well developed and fairly well nourished, complaining of the coldness of the ward. His skin was white and covered with dry, oily scales. His thorax was long, narrow and rather full. The respiratory movements were normal. The cardiac impulse was in the fifth interspace, 13 cm. to the left of the midsternal line, the left border 15 cm. out in the fifth interspace, the right border 3.5 cm. to the right of the midsternal line, the upper border at the third rib. At the apex the sounds were slow and regular, the first sound sharp and preceded by a soft presystolic murmur and followed by a long, blowing diastolic murmur which was transmitted into the axilla. A short systolic murmur was heard in the aortic area, loudest in the second right interspace and not transmitted. The peripheral vessels were tortuous and easily palpated. There was a Corrigan pulse but no Duroziez' sign.

In the lungs were many fine crackling râles along the lower borders. The abdomen was scaphoid and there was shifting dulness in the flanks. There was a sense of resistance in the epigastrium, but no definite mass was felt, nor were there any areas of tenderness. The liver dulness extended from the fifth rib to the costal margin. The spleen and kidneys could not be felt. The penis and scrotum were edematous. The legs showed moderate soft edema.

Clinical Pathology.—Hemoglobin (Sahli), 63 per cent.; erythrocytes, 3,700,000. Smear showed no abnormal forms. The urine contained a slight trace of albumin and a moderate number of hyaline casts. The phenolsulphonephthalein output was 42 per cent. in two hours. Clinical diagnosis, chronic cardiac valvular disease, aortic insufficiency, syphilitic aortitis (?), secondary anemia, chronic nephritis. He was given digitalis leaves, 0.1 gm. four times a day.

The following day a capillary pulse was noted in his finger nails. January 29, temperature, pulse and respiration were normal. After twelve doses of 0.1 gm. digitalis leaves, diuresis occurred with a loss of 6.4 kg. The blood Wassermann reaction was double plus. Gastric analysis showed anacidity. The edema of the extremities was much decreased but had not entirely disappeared.

February 6. Roentgen report: "Negative gastro-intestinal findings. In the gallbladder region there is a suggestive shadow, but not sufficient to be due to a calculus."

February 12. The urine contained the slightest possible trace of albumin but no erythrocytes or casts. He had lost 12 pounds in weight and complained of "weakness of stomach." He would have liked to eat more but could not. His speech was rambling.

February 14. Edema was more marked in the right leg than in the left. The glands in the right groin were enlarged and tender. The right saphenous vein for one third the distance to the knee was very tender. Apparently thrombosis of the saphenous vein could account for the unilateral edema.

February 20. Blood pressure: systolic 150, diastolic 80.

February 23. The abdominal veins were enlarged, the blood flowing from below upward. There was marked edema of the right leg and slight edema of the left leg. The abdomen was rather full, especially the upper part. No masses were felt. The signs were those of obstructed inferior vena cava.

February 27. Blood pressure: systolic 130, diastolic 80.

April 2. Blood pressure: systolic 140, diastolic 80.

April 4. There was a definite fluid wave in the flanks. The liver edge suddenly became palpable 9 cm. below the costal margin in the right mammary

line. He had a strong "acetone" breath and vomited frequently. The respirations were of the character of acidosis.

He later became comatose. Alveolar air carbon dioxid tension 11.6 mm. Hg; temperature 97 F. He was given 3 per cent. sodium bicarbonate in

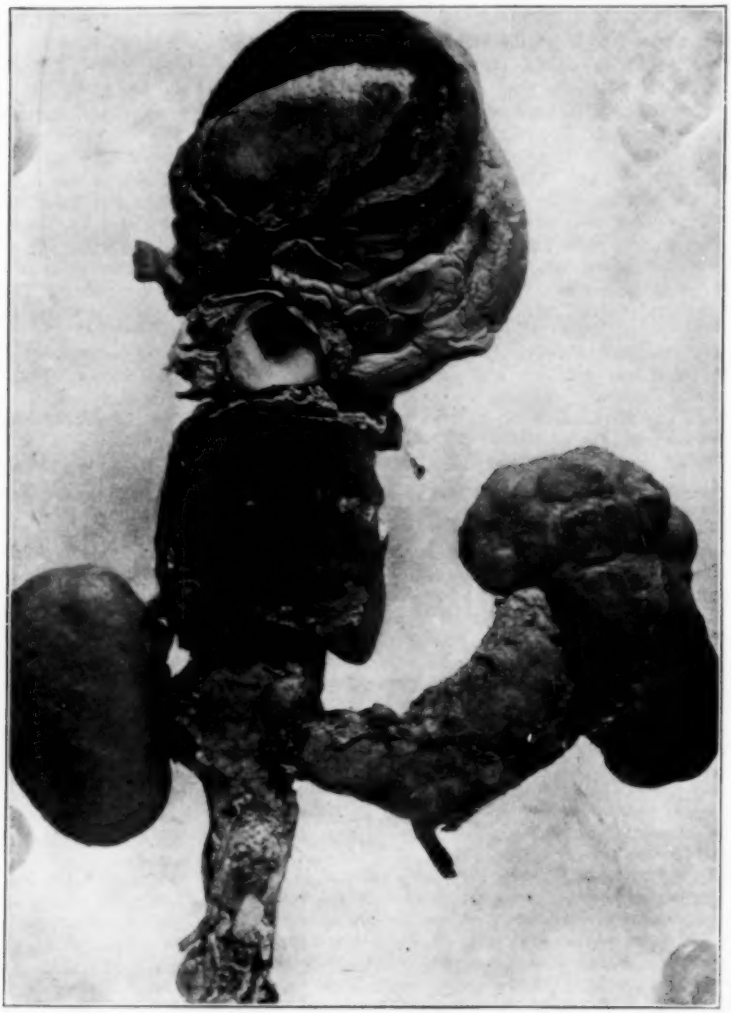


Fig. 1.—Anterior view of authors' specimen.

physiologic sodium chlorid solution per rectum by Murphy drip. Catheter specimen of urine, 500 c.c., showed a moderate amount of diacetic acid. Shortly after 6 p. m. his respirations slowed down and stopped.

Necropsy.—Performed sixteen hours postmortem by Dr. E. W. Goodpasture.

Diagnoses.—Hypernephroma of left kidney with invasion of left renal vein, inferior vena cava and one of right renal veins; occlusion of inferior vena cava; metastases to liver and lungs; multiple diverticuli of duodenum and jejunum; aortic arteriosclerosis; hypertrophy of heart, left; dilatation of aortic ring; congestion of liver; ascites and bilateral hydrothorax; edema; fatty degeneration of heart; bronchopneumonia.

Body: The body was that of a large framed, middle aged, white man, showing considerable emaciation. The tissues were flabby and there was considerable edema of extremities, the legs pitting easily on pressure. The thorax was barrel shaped, abdomen protuberant.

Peritoneal Cavity: Contained 180 c.c. of clear yellow fluid; liver extended two fingers' breadth below the costal margin in the right mammary line; diaphragm on both sides at fourth interspace.

Thoracic Cavity: Lungs were voluminous, each covered largely by thin, tough, fibrous adhesions; 300 c.c. clear yellow fluid in each pleural cavity.

Heart: Enlarged, especially the left side; mitral ring measured 9 cm., aortic 8.25 cm.; aortic valve was normal except for extensive thickening about the corpora arantii and glueing together and calcification between the posterior and right cusps; myocardium was very flabby and pale yellow; heart was left in situ because of necessity of careful dissection of inferior vena cava which was filled with tumor growth extending into the right auricle.

Lungs: Voluminous; lateral portion of right lung and anterior portion of left lung were covered by fibrous adhesions. On the surface of each lung a great number of yellow, firm tumor nodules up to 2 cm. in diameter, for the most part smaller, were scattered irregularly over the surface. On section similar tumors were found scattered throughout the lung substance. The tumor masses were rather opaque on the cut surface, very soft and grayish-yellow in color. Sometimes the centers were soft and yellow, while the peripheries were more translucent. A yellow opaque center was often surrounded by a red zone and the peripheral gray tissue appeared to be vascular.

Gastro-Intestinal Tract: The duodenum was normal for 6 cm. beyond the pylorus. At this point there was a diverticulum lying just over the head of the pancreas, 2.5 cm. in diameter. Just opposite Treitz' ligament was another diverticulum measuring 2.5 cm. in diameter, and 6 cm. below was a very large diverticulum 5 cm. in diameter. All opened into the intestine, as could be determined by squeezing air from them into the intestine. Beyond the largest were a dozen smaller in the fat of the mesenteric attachment for a distance of one foot.

Liver: Larger than normal, dark purple. On section lobulation was distinct, centers purple, depressed, portal areas grayish yellow. The hepatic veins from the largest to the smallest were plugged with dark, purple thrombi. In the middle anterior portion of the left lobe a small mass was found measuring 5 mm., with a grayish pink center and yellowish periphery, which appeared to be a tumor metastasis.

Tumor: A large mass occupying the region of the left kidney on section was found to be a hypernephroma occupying the upper two-thirds of the kidney substance. It measured 10 cm. in length and 8 cm. in width. The surface of the kidney in the region of the tumor was lobulated and the capsule was very vascular. On section through the tumor it presented a yellow, opaque surface composed of tissue resembling adrenal cortex. Numerous small hemorrhages were scattered throughout the tumor and there was a pink tone to the tumor tissue, indicating great vascularity. Brighter yellow opaque areas were scattered through the tumor which appeared to be areas of necrosis.

The right kidney was of normal size. The capsule was smooth, stripped easily, leaving a slightly irregular surface. The left renal vein was tremendous. It was plugged and distended with soft yellow tumor tissue, and measured 12 cm. in length and 5.5 cm. in diameter. The inferior vena cava was completely plugged with tumor growth both in the upper and lower portions, from

the origin of this renal vein. In its upper portion, however, it was very greatly dilated, being 5.5 cm. in diameter, the lower portion 3 cm. in diameter, and became attenuated as the pelvis was approached. Both internal iliac veins were plugged with tumor thrombi. The tumor extended upward in the vena cava into the right auricle and ventricle, but the great distention of the vein

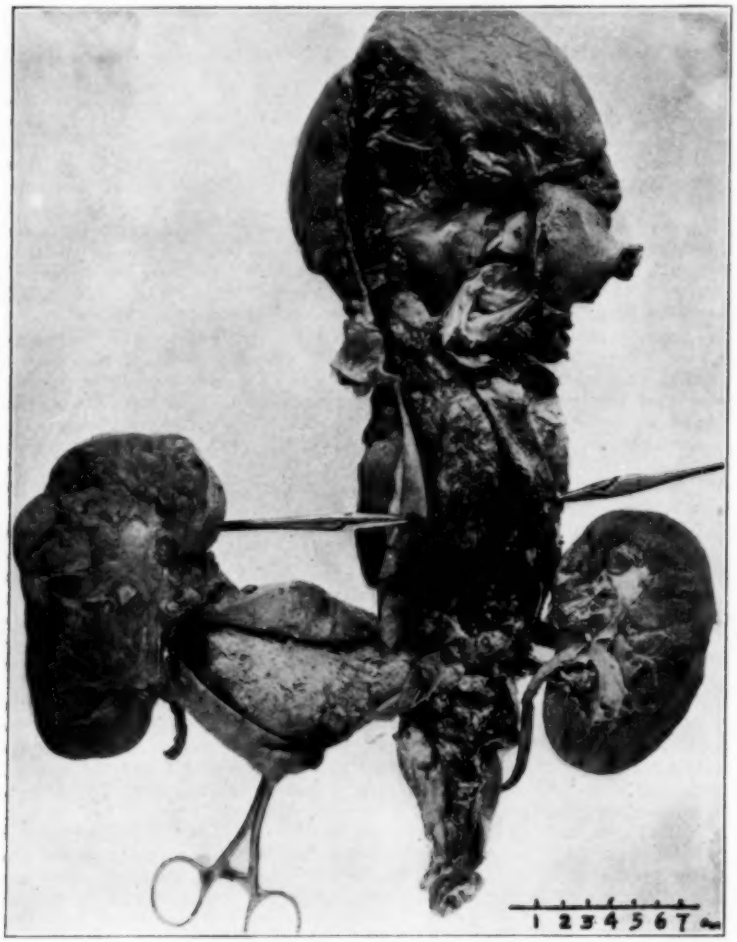


Fig. 2.—Posterior view of specimen.

ended at the diaphragm. Above this point it measured 2.5 cm. in width. The right renal veins were two in number and about normal in size. The superior vein, 1 cm. in diameter, was patent in its entire length. The inferior right vein was 0.5 cm. in width, deep purple and quite solid. The pelvis of each kidney and the ureters were normal.

Adrenals: Normal in size and normal in general. The left adrenal could be almost completely dissected out from the tumor about its superior surfaces, but inferiorly, next to the kidney, it was invaded by tumor mass and could not be separated from it. The perirenal fat of the left kidney was very thick and firm. On section this fat showed evident tumor extension in the connective tissue between the fat lobules, but the rigidity of the fat did not appear to be due entirely to tumor growth, but probably to connective tissue thickening between the fat lobules. There was some fat of yellow, opaque appearance, rather than translucent.

Pelvic Organs: The vessels about the prostate were thrombosed.

Microscopical Examination.—Left Kidney: The tumor is composed chiefly of polyhedral cells with pale or clear, vacuolated cytoplasm. The nucleus, containing one or two basophilic nucleoli, is centrally or eccentrically placed. The cells are arranged chiefly in alveolar form, but columnar formation is also present. In some sections tubular architecture is strikingly predominant, strongly suggesting renal tubules. There are many large and small vascular spaces lined with a single layer of flat epithelium and containing much blood. There are many small thrombi undergoing hyalinization. The tumor is not sharply marked off from the renal substance proper. The cortex of the kidney shows much fibrosis and hyalinization of glomeruli and obliteration of the normal tubular arrangement. Sections of the tumor from the renal pelvis show a less differentiated type and arrangement of the cells, the latter tending to be more spindle shaped than polyhedral.

Right Kidney: Chronic passive congestion and moderate amount of fatty change in convoluted tubules.

Lung: There are many scattered small nodules of tumor tissue which occupy alveoli, the walls of which are thickened. There is marked chronic passive congestion.

Spleen: Shows chronic passive congestion.

Liver: There are obliterating thrombi in the tributaries of the hepatic veins and extensive central necrosis of the liver substance with hemorrhagic infiltration in the necrotic areas. The normal columnar architecture is retained only at the peripheral portions of some of the lobules. There is very little polymorphonuclear reaction within the areas of necrosis. Sections of the thrombi from the hepatic veins show no tumor tissue, and the thrombi are apparently of recent origin, with the exception of one in the quadrate lobe in which organization has begun.

Bone Marrow: The bone marrow is hyperplastic.

Thrombus: Section of the thrombus from the inferior vena cava and right auricle show almost solid infiltration with tumor cells, with little tendency to any definite arrangement. There is great variation in size, shape and intensity of staining of the individual cells.

The thrombi from the right renal veins contain no tumor tissue.

Sections of the thrombi occluding the caval orifices of the hepatic veins show no tumor tissue. The thrombus in the vein draining the quadrate lobe shows beginning organization; those involving the right and left lobes are apparently about twenty-four hours old.

Portions of the thrombus from 4 cm. below the iliac bifurcation in the right and left common iliac veins contain a few strands of tumor cells, which, however, are more spindle-shaped and not vacuolated, corresponding more to the morphology of the tumor cells in the cardiac thrombus.

In the left renal vein, just proximal to the caval orifice, sections of the tumor mass show a strikingly tubular arrangement of tumor cells, but no basement membrane was demonstrable with Mallory's phosphotungstic acid-hematoxylin stain.

Pleasants,[1] in 1911, was able to collect 314 cases of obstruction of the inferior vena cava. Of this number 171 were due primarily to thrombosis, the majority of which were associated with inflammatory foci elsewhere in the body. Obstruction due to new growths (*Geschwulst-thrombose*) occurred 88 times; by invasion, 48; by pressure, 21; and by thrombosis, 19. Due to new growths in the kidney, 29 times, classified as follows: carcinoma, 21 times, causing invasion 12, pressure 2 and thrombosis 6 times. Sarcoma 8 times, causing invasion 5, pressure 2 and thrombosis 1 time. Due to new growth in the suprarenal gland, 3 times; sarcoma, 3 times, causing invasion 1, pressure 1, and thrombosis 1 time. Invasion was found to be most frequent in the middle third of the cava and the most common path of invasion was through the renal veins, and in an upward direction. Obstruction by pressure from without arose most frequently also in the middle third, owing to the nearness of the liver and other structures. Thrombosis was commonest in the lower third but also occurred in the upper and middle thirds through disease of the affluent veins.

Of the cases of *Geschwulst-thrombose,* in 43 cases accurately described, Pleasants found the lower third alone occluded in 9 cases and lower and middle thirds together in 7 cases; the middle third alone in 6 cases and the middle and upper thirds together in 17 cases. In only one instance was the entire cava from the iliacs to the right auricle filled. In 13 cases the growth reached as far as the right auricle or actually invaded it.

The most striking symptoms or physical signs of obstruction of the vena cava encountered were, lumbar pain, edema of the lower extremities and abdominal wall, and the establishment of collateral circulation. All of these features were found to depend on the position, extent, rapidity and completeness of the obstruction. The most strikingly developed of the superficial collateral circulatory routes was the superficial inferior epigastric-internal mammary channel. This was the collateral channel shown in our case. In many instances, with no superficial routes evident, the blood reaches the heart through deep vessels, the most frequent way being through the internal iliac-ascending lumbar-azygos-superior vena cava anastomosis.

There are several extraordinary features in our case: (*a*) The remarkable extension of the tumor from the upper pole of the left kidney to the left renal vein to the inferior vena cava which it traversed below as far as the iliac bifurcation and grew upward into the right auricle and right ventricle, causing mechanical embarrassment to the tricuspid valve. The nodules in the lungs were most likely derived from emboli from this portion of the tumor. Of the right renal veins

1. Pleasants: Johns Hopkins Hosp. Rep., 1911, **16,** 363.

(there being two), the inferior one was distended with red thrombus extending in from the inferior vena cava as far as the renal pelvis. The orifices of the hepatic veins were plugged with the tumor and metastases were present in the liver substance. (*b*). The first noticeable symptoms occurred seven and one-half months before death. They were in the nature of loss of appetite, sense of fullness after eating, and gastro-intestinal discomfort of more or less vague character. Edema of the legs and scrotum appeared five months later, during which time there was a loss in weight of 70 pounds. However, the patient was able to attend to his work right up to the time of his entrance to the hospital, where he came merely to get "rested up." (*c*). The absence of hematuria. (*d*). The late appearance of definite signs of obstruction of the inferior vena cava in spite of the fact that that vessel was occluded in its entire length at necropsy. (*e*). The acute swelling and centro-acinous necrosis of the liver from thrombosis of the hepatic veins and death in acidosis. The sudden enlargement of the liver noted clinically was probably associated with the hepatic thrombosis.

Metastases in hypernephroma are frequently extensive. Growth of the tumor along the renal vein to the inferior vena cava from the affected kidney is not so common. Ribbert[2] in his *Geschwulst Lehre* mentions a case in which the tumor ascended the inferior vena cava to the right auricle without obstructing the hepatic veins. J. Israel[3] and Rolleston[4] have reported instances of invasion of the inferior cava, the latter's case being secondary carcinoma of the right suprarenal, extending in along the capsular vein.

The remarkable patient of Parkes Weber[5] showed symptoms of obstructed inferior vena cava, enlarged liver and spleen, and ascites. The last two days there occurred anuria, uremia, coma and death. Necropsy disclosed a thrombus-containing tumor (papilliferous adrenal carcinoma) commencing in the left renal vein, involving both renal veins, both hepatic veins, the whole of the inferior cava, with the upper end projecting into a partially occluded right auricle. Both adrenals and kidneys were infiltrated with "malignant hypernephroma." Nodules of tumor were present in the liver and lungs. The liver also showed the central necrotic changes of extreme passive congestion. Death occurred from thrombosis of the better kidney with resultant anuria and uremia.

Herbert French[6] has described a case of carcinoma of the left kidney with a continuous clot of tumorous tissue extending along the left renal

2. Ribbert: Geschwulste Lehre, 1904, p. 35.
3. Israel: Deutsch. Med. Wchnschr., 1904, **30,** 489.
4. Rolleston and Marks: Am. Jour. Med. Sc., 1898, **116,** 404.
5. Weber, Parkes: Proc. Royal Soc., 1915, **8,** 6.
6. French: Tr. Med. Soc., London, 1912, **35,** 243.

vein, up the inferior vena cava into the right auricle, producing an intracardiac polypoid mass leading to tricuspid stenosis of the ball and socket type. Rolleston[7] quotes Adami as having seen a similar extension of adrenal tumor.

Other neoplasms, such as carcinoma and teratoma of the testis,[8] have produced extensive deposits in the inferior vena cava. Thrombosis may give rise to a similar train of symptoms from occlusion of the inferior cava, hepatic veins and extension into the right auricle.

The symptoms produced by simple occlusion of the hepatic veins are not always very definite. The syndrome of Craven Moore,[9] progressive enlargement of the liver, signs of involvement of the inferior vena cava and ascites, is mentioned by Osler[10] as being characteristic of stenosis of the orifices of the hepatic veins. In Chiari's[11] three cases which had a luetic background, death occurred from ascites and pulmonary edema. Winternitz[12] ligated an hepatic vein in a dog and observed no untoward effect or any macroscopic or microscopic changes in the liver.

In our case, twenty four hours before death the liver suddenly became greatly enlarged, the patient developed symptoms of acute acidosis with strong "acetone" breath, alveolar air carbondioxid tension of 11.6 mm. Hg, and diacetic acid was found in the urine. The central necrosis of the liver lobules and the thrombi behind the tumor tissue in the orifices of the hepatic veins appeared to be about twenty-four hours old.

The sudden enlargement of the liver coincident with the onset of acidosis suggests a point which may be of diagnostic significance in acute thrombosis of the hepatic veins, where there are already signs of obstruction of the inferior vena cava.

The more rapid cases of hepatic obstruction give a picture which much resembles myocardial failure, there being present cyanosis, congestion of the lungs, enlarged tender liver, and ascites.[13] The rarity of thrombi in the hepatic ostia has been attributed to the marked obliquity of the veins and also to the diminished coagulability of the hepatic blood.[14]

The structure of the tumor in our case is interesting in that the tubular arrangement of the cells is quite the predominating architecture in some sections and the individual cells are strikingly like those

7. Rolleston: Diseases of Liver and Bile Ducts, 1912, p. 498.
8. McCallum: Textbook of Pathology, 1916, p. 1010.
9. Craven Moore: Med. Chron. Series 4, 1902, **3**, 240.
10. Osler: The Principles and Practice of Medicine, 1915, 563.
11. Chiari: Zeigler's Beitr. z. Path. Anat. u. z. Allg. Path., 1899, **26**, 1.
12. Winternitz: Bull. Johns Hopkins Hosp., 1911, **22**, 396.
13. Thompson and Turnbull, Quart. Jour. Med., 1912, **5**, 277.
14. Kretz: Ergebn. d. allg. Path., 1902, **8**, 498.

of normal renal tubules, being cuboidal and with granular cytoplasm instead of being vacuolated. There are all gradations between the cells of the normal kidney tubule and the more primitive, less differentiated, heavily fat-laden cell of typical hypernephroma.

SUMMARY

Occlusion of the inferior vena cava by new growth (*Geschwulstthrombose*) is rare, up to 1911 there having been but forty-three cases accurately described. In thirteen of these the growth reached as far as the right auricle or actually invaded it. In only one instance was the entire cava from iliacs to right auricle filled. Since then several other instances of obstruction by intravascular new growth have been reported, two of which showed occlusion from the level of the renal veins with tumor projecting into the right auricle. In one case the tumor tissue completely filled the inferior vena cava and extended into the right auricle.

The case reported here is one in which a renal hypernephroma extended from the kidney into the left renal vein, traversed the inferior vena cava below as far as the iliac bifurcation and grew upward into the right auricle and right ventricle causing mechanical embarrassment to the tricuspid valve.

The orifices of the hepatic veins were plugged with tumor, and there was acute central necrosis of the liver from thrombosis of the hepatic vein and its branches. Sudden enlargement of the liver was accompanied by the onset of acidosis which persisted until the death of the patient twenty-four hours later.

Where there are already signs of obstruction of the inferior vena cava, sudden enlargement of the liver coincident with the onset of acidosis is probably indicative of acute thrombosis of the hepatic veins.

ALIMENTARY RENAL GLYCOSURIA*

KINGO GOTO, M.D.
NEW YORK

INTRODUCTION

The glucose content of normal human urine is under 0.1 per cent., usually merely a trace. The kidneys normally excrete urine containing a lower concentration of glucose than is found in the blood. When the kidneys show a higher permeability for glucose, sugar should appear in the urine while the tissues still retain the normal power of utilizing dextrose. So-called "renal glycosuria" occurs on account of an abnormal permeability of the kidneys, without any disturbance of intermediary carbohydrate metabolism. In such a condition there are no diabetic symptoms and the blood sugar is normal.

The existence of this condition was first declared by Klemperer[1] at the Congress of Internal Medicine, in Berlin, 1896, and the conditions for its diagnosis were given as follows:

1. The glycosuria has almost no relation to the quantity of carbohydrate in the diet.

2. Not only is there no hyperglycemia, but sometimes even hypoglycemia.

3. When nephritis occurs the sugar in the urine diminishes or disappears.

Vo Noorden,[2] in his book, "Zuckerkrankheit," refused to recognize the cases of renal diabetes previously reported, and held that the condition had not been demonstrated. Allen,[3] who recognizes renal glycosuria, in his book, "Glycosuria and Diabetes," says that "the name diabetes is unjustifiable, diabetic symptoms are absent, but those of nephritis, neurasthenia and malnutrition are frequent;" and again, "almost always the glycosuria is very slight, a mere fraction of 1 per cent." Joslin[4] recognized renal glycosuria and declared that an observation of several years was necessary for its diagnosis, clinical diagnosis without long observation of the patient being dangerous.

---

* Submitted for publication April 24, 1918.

* From the Hospital of the Rockefeller Institute for Medical Research.

1. Klemperer, G.: Cong. Int. Med., Berlin, 1896. Ueber Regulatorische Glykosuria u. renalen Diabetes, Berl. klin. Wchnschr., 1896, **33**, 571.

2. Von Noorden, C.: Die Zuckerkrankheit und ihre Behandlung, Ed. 6, Berlin, 1912, p. 37.

3. Allen, F. M.: Glycosuria and Diabetes. 1913.

4. Joslin, E. P.: Treatment of Diabetes Mellitus. 1917.

Since the initial report of Klemperer, a few reports of cases have been made in Germany by Lüthje,[5] Bönninger,[6] Weiland,[7] Tachau,[8] Frank,[9] de Langen,[10] and Galambos;[11] and in America recently by Lewis and Mosenthal,[12] Murlin and Niles[13] and Strouse.[14] The details of these reports will be included in the chapter of discussion.

REPORT OF CASE

As renal glycosuria is considered rare, observations on one case are here reported as follows:

History.—Man, aged 33, Japanese physician. No diabetic or neuropathic heredity; healthy childhood; at the age of 22 the patient had typhoid fever in the course of which albumin and casts were found in the urine for about two weeks. After university graduation in 1909, he was assistant at the university hospital. He was healthy; no complaint; of good nutrition; body weight, 50 kg.; height, 161 cm. Since 1911, his weight gradually increased to 54 kg.; there was increasing appetite, particularly for sweets; besides regular diet, cakes containing about 50 to 70 gm. of sugar were eaten once and sometimes twice in the afternoon. In April, 1913, after a meal consisting of 200 gm. rice, 150 gm. meat, vegetables cooked with sugar, after Japanese fashion, and much candy, an examination of the urine passed within two hours revealed 0.75 per cent. sugar. The determination of sugar in the urine was made qualitatively by the Almen-Nylander method, and quantitatively by Kumagawa and Suto's modification of Pavy's method. On the following day, after a lunch of 50 gm. bread and tea, the urine showed a slight sugar reaction. On the third day, after keeping in the meantime to carbohydrate-free diet, the urine showed no sugar reaction after a meal of 30 gm. bread; but after a lunch of 60 gm. bread, the glycosuria was present. He considered himself diabetic and treated himself accordingly. After eating 60 gm. bread at one time, sugar regularly appeared in the urine passed within two hours. The percentage of sugar was always below 0.7.

From June to November, 1913, a diabetic diet was followed. Sugar was excluded, but about 30 gm. carbohydrate in the form of bread and rice were taken with each meal, or from 90 to 100 gm. daily. The urine, examined

5. Lüthje, H.: Beitrag zur Frage des renalen Diabetes, München. med. Wchnschr., 1901, **38,** 1471.

6. Bönniger, M.: Beitrag zur. Frage des Nierendiabetes, Deutsch. med. Wchnschr., 1908, **34,** 780.

7. Weiland, W.: Ueber einige ätiologisch bemerkenswerte Diabetesformen, Deutsch. Arch. f. klin. Med., 1911, **102,** 167.

8. Tachau, H.: Beitrag zum Studium des Nierendiabetes, Deutsch. Arch. f. klin. Med., 1911, **104,** 448.

9. Frank, E.: Ueber experimentelle u. klinische Glycosurien renalen Ursprungs, Arch. f. exper. Path. u. Pharmakol., 1913, **72,** 387 and 443.

10. de Langen, C. D.: Beitrag zur Kasuistik des renalen Diabetes, Berl. klin. Wchnschr., 1914, **51,** 1792.

11. Galambos, A.: Ueber den renalen Diabetes, Deutsch. med. Wchnschr., 1914, **40,** 1301.

12. Lewis, D. S., and Mosenthal, H. O.: Renal Diabetes, Bull. Johns Hopkins Hosp., 1916, **27,** 133.

13. Murlin, J. R., and Niles, W. L.: Renal Glycosuria, Am. Jour. Med. Sc., 1917, **153,** 79.

14. Strouse, S.: Renal Diabetes, Med. Clinics of Chicago, 1916, **2,** No. 2, p. 239.

from time to time showed an occasional sugar reaction From January, 1914, the strict diabetic diet was remitted, but no sugar was taken; the diet included from 150 to 200 gm. carbohydrate daily, in the form of rice and vegetables. For a period of two years, the urine was not examined. Beginning April, 1916, after coming to America, sugar was added to the diet according to inclination, in the form of candy and ice cream. During this time the subject felt well and experienced no weakness. Sept. 17, 1917, examination of the urine after the ordinary lunch showed almost 0.2 per cent. sugar. The determination of sugar in the urine was made qualitatively and quantitatively by Benedict's method.[15] From September 20 to October 15, the diet consisted approximately of 100 gm. fat, 150 gm. carbohydrate, and from 150 to 200 gm. protein per day. Sugar was excluded; the urine showed no sugar reaction. But on a free diet containing sugar the urine two hours after meals occasionally showed a slight sugar reaction, not more than 0.2 per cent. The urine volume was not increased, and no sugar reaction was seen with mixed twenty-four-hour urine.

Experimental.—October 20, blood was taken at 9 a. m., before breakfast, after fasting over night, and determination of sugar in the blood made by the method of Lewis and Benedict;[16] cholesterol in whole blood by Bloor's method,[17] and carbon dioxid in the plasma by Van Slyke's method.[18] All showed normal. The blood pressure was also normal.

TABLE 1.—Findings in Plasma and Whole Blood Oct. 20, 1917, at 9 P. M., Before Breakfast, After Fasting Over Night

Sugar in Plasma, Per Cent.	Cholesterol in Whole Blood, Gm. per 100 C.c.	CO_2 Capacity of Plasma, Vol. Per Cent.
0.11	0.22	74

From November 29, every morning a certain amount of carbohydrate was ingested after the night's fast, with results as follows: After 33 gm. starch and 25 gm. fat, no sugar appeared in the urine, but with increase of starch to 39 gm., sugar appeared one or two hours after meals, but in quantities so slight that it was hard to estimate its percentage by Benedict's quantitative method. Blood sugar was examined for every thirty minutes after meals, but no hyperglycemia appeared. After ingestion of 150 gm. banana (34 gm. carbohydrate), the urine showed sugar, presumably because of the sugar content of

15. Benedict, S. R.: The Detection and Estimation of Glucose in Urine, Jour. Am. Med. Assn., 1911, **57,** 1193.

16. Lewis, R. C., and Benedict, S. R.: A Method for the Estimation of Sugar in Small Quantities of Blood, Jour. Biol. Chem., 1915, **20,** 61.

17. Bloor, W. R.: The Determination of Cholesterol in Blood, Jour. Biol. Chem., 1916, **24,** 227. The Distribution of the Lipoids (Fat) in Human Blood, Jour. Biol. Chem., 1916, **25,** 577.

18. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: Studies of Acidosis, Jour. Biol. Chem., 1917, **30,** No. 2, p. 289.

the banana. After 50 bm. oatmeal (34 gm. carbohydrate), the urine showed sugar in two hours, but the blood sugar was normal. After 150 gm. potato (36 gm. carbohydrate), there was glycosuria in one hour, but no hyperglycemia. Therefore, after the ingestion of more than 34 gm. carbohydrate, the urine showed sugar after meals, without regard to the kind of starch taken, while the blood sugar was always normal.

In the third experiment (Table 3), large quantities of carbohydrate were ingested to determine the rise of blood sugar.

After the ingestion of 130 gm. rice (carbohydrate about 100 gm.), the urine showed from 0.16 to 0.29 per cent. sugar, which lasted to the fourth hour after meals. The total sugar excreted amounted to 0.25 gm. Blood sugar, which reached its maximum in the first hour, amounted only to 0.115 per cent. No hyperglycemia was seen. After ingestion of 200 gm. starch, the urine showed from 0.2 to 0.3 per cent. sugar which lasted for 2.5 hours. The total amount of sugar excreted was 0.17 gm. Blood sugar reaching its maximum in 2.5 hours was 0.145 per cent. Sugar appeared in the urine after thirty minutes, when the blood sugar showed only 0.139 per cent.

In the fourth experiment (Table 4), glucose was taken in various quantities, in the morning as in the former experiments.

After 50 gm. glucose, sugar appeared in the urine in 30 minutes to 1.5 hours, the total amount being 0.07 gm. The maximum of blood sugar was 0.128 per cent., with return to normal at the end of the first hour. After 100 gm. glucose, sugar appeared in the urine at 30 minutes to 1.5 hours with a total amount of 0.9 gm.; blood sugar reached its maximum at 0.164 per cent. with return to normal within 3 hours. After 200 gm. glucose, sugar appeared after 30 minutes and lasted 4.5 hours, with a total excretion of 0.6 gm.; the maximum of blood sugar was 0.175 per cent. with return to normal at the third hour. Examination of the urine by polarimeter showed dextrorotation and agreed with the results obtained by Benedict's method. A fermentation test with yeast gave positive results, showing that the reducing substance in urine is glucose, not pentose. After the ingestion of 100 gm. levulose, the urine showed sugar after 30 minutes and continuing for 3 hours, with a total excretion of 0.09 gm. The polarimeter showed left rotation, blood sugar, a maximum of 0.143 per cent., with return to normal in the second hour.

Summary.—After the ingestion of more than 34 gm. starch, the urine showed sugar without any hyperglycemia; after 100 gm. starch the urine contained 0.25 gm. sugar, while after 200 gm. starch the urine showed only 0.17 gm. sugar; the maximum of blood sugar was 0.115 per cent. after ingestion of 100 gm. starch and 0.145 per cent.

TABLE 2.—Determination of Carbohydrate Tolerance.—

Date, 1917	Diet (Test meals at 9 a. m. after fasting over night)							Urine			
	Foodstuffs, Gm.					Carbohydrate, Gm.	Fat, Gm.	Volume, C.c.			
	Bread	Butter	Coffee	Cream	Salt			1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
Nov. 29	45	30	2 cups	...	...	27	25	53	40	24	31
Nov. 30	55	30	2 cups	...	1	32	25	45	39	21	20
Dec. 1	65	30	2 cups	...	1	39	25	46	28	25	30
Dec. 2	Banana 150	...	2 cups	...	...	33	...	44	40	23	28
Dec. 3	Oatmeal 50	30	2 cups	30	1	34	31	50	33	40	30
Dec. 4	Potato 150	30	2 cups	30	1	36	31	51	42	36	21

* Sugar test by Benedict's method, shows very slight reduction, qualitatively not measurable.

TABLE 3.—Starch Test. Test Meals—

Date, 1917	Diet (Test meals at 9 a. m. after fasting over night)							Urine								
	Foodstuffs, Gm.					Carbohydrate, Gm.	Fat, Gm.	Volume, C.c. Dextrose								
		Butter	Coffee	Cream	Salt			30 Min..	1 Hr.,	1.5 Hr.,	2 Hrs.,	2.5 Hrs.,	3 Hrs.,	3.5 Hrs.,	4 Hrs.,	4.5 Hrs.,
Dec. 5	Rice, 130 gm. (dry weight), boiled with 100 gm. water	30	2 cups	30	4	100	31	.. ..	42 +	.. ..	27 +	.. ..	23 +	.. ..	20 +	16 —
Dec. 14	Starch (Merck), 200 gm. Paste made with 100 gm. water	..	2 cups	...	..	200	..	45 +	8 +	15 +	6 ±	9 +	11 —	10 —	8 —	7 —

TABLE 4.—Sugar Test. Sugar at—

Date, 1917	Glucose, Gm.	Water, C.c.	Urine												
			Volume, C.c. Dextrose									Sugar in Hours, Per Cent. Total Quantities Sugar, Gm.			
			30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	4.5 Hrs.	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
Dec. 19	50	300	30 +	15 +	16 ±	30 —	22 —	.. —	.. —	.. —	.. —	0.14 0.063	....	....	....
Nov. 1	100	500	182 +	100 +	42 +	76 —	50 —	.. —	.. —	.. —	.. —	0.32 0.68	0.16 0.16	....	....
Dec. 26	200	300	11 +	8 +	.. ..	17 +	6 +	6 +	5 +	4 +	3 ±	1.26 0.24	1.08 0.19	0.99 0.12	0.39 0.04
Dec. 8	Levulose 100	300	35 +	12 +	4 +	11 +	6 +	21 +	23 —	.. ..	.. ..	....	....	....	....

—Test Meals at 9 a. m., After Fasting Over Night

Urine				Blood								
Dextrose				Sugar in Whole Blood, Per Cent.								Remarks
1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	
—	—	—	—	....	....	....	....	....	....	....	....	
—	—	—	—	....	....	....	....	....	....	....	....	
—	Trace*	—	—	0.081	0.085	0.087	0.082	0.085	0.086	....	0.071	
Trace	—	—	—	....	....	....	....	....	....	....	....	
—	Trace	—	—	....	....	....	0.071	....	....	....	....	Sugar in plasma in 1.5 hr., 0.102 per cent.
Trace	Trace	—	—	....	....	....	0.081	....	....	....	....	

—at 9 a. m., After Fasting Over Night

Urine					Blood									
Sugar in Hours, Per Cent. Total Quantities Sugar, Gm.				Excreted Sugar	Sugar in Whole Blood, Per Cent. Sugar in Plasma, Per Cent.									
1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	in Toto	Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.	5 Hrs.
0.16	0.26	0.29	0.18	= 0.25 gm. Polarimetric 0.19 per cent.	0.076	....	0.069	....	0.058	....	0.057	....	....	0.055
0.067	0.07	0.067	0.04		0.108	....	0.115	....	0.111	....	0.083	....	....	0.085
0.20	0.3	....	....	= 0.17 gm.	0.08	0.122	....	0.105	....	0.118	....	0.093	....	....
0.106	0.06	....	....		0.105	0.139	....	0.133	....	0.145	....	0.102	....	....

—9 a. m., After Fasting Over Night

Total Sugar Excreted	Blood								
	Sugar in Whole Blood, Per Cent. Sugar in Plasma, Per Cent.								
	Before Test	30 Min.	1 Hr.	1.5 Hrs.	2 Hrs.	2.5 Hrs.	3 Hrs.	3.5 Hrs.	4 Hrs.
	0.082	0.085	0.095	....	0.088	....	....	....	....
= 0.07 gm.	0.097	0.128	0.116	....	0.094	....	....	....	....
	Plasma	....	....	....	....	....	....	....	....
= 0.9 gm.	0.09	0.164	0.135	0.123	0.131	....	0.095	....	....
= 0.6 gm.	0.081	0.112	0.099	....	0.098	....	0.082	....	0.097
0.92 per cent. in toto Polarimetric 0.83 per cent.	0.091	0.175	0.133	....	0.121	....	0.105	....	0.133
0.09 gm. 0.105 per cent.	0.072	0.071	0.061	....	0.094	....	0.061	....	....
Polarimetric left rotation 0.098 per cent.	0.101	0.143	0.128	....	0.106	....	0.114	....	....

after 200 gm. starch. Furthermore, after the ingestion of 100 gm. glucose, more sugar was excreted in the urine than when 200 gm. were taken, while the blood sugar was higher and remained higher for a longer period after 200 gm. glucose was ingested than after 100 gm. When levulose was given it was excreted as levulose itself, not as glucose.

The Renal Threshold for Glucose.—There are many reports concerning the renal threshold for glucose of the normal person. It is generally accepted that the kidney is permeable for sugar when the blood sugar reaches 0.16 to 0.17 per cent. Hamman and Hirschman[19] say that in a normal individual the renal threshold is not a constant factor, but is usually between 0.17 and 0.18 per cent. of blood sugar, although some otherwise normal individuals have a low renal threshold, below 0.14 per cent. (0.12 to 0.14 per cent., or 0.13 to 0.14 per cent.). Foster[20] found the renal threshold between 0.149 and 0.164 per cent. in a patient who had undergone ether narcosis. Jacobsen[21] gives the blood concentration as 0.16 to 0.17 per cent. In the person reported on here, the renal threshold is as follows: whole blood, 0.069 to 0.071 to 0.081 to 0.085 per cent.; plasma, 0.115 per cent.

Hyperglycemia After the Intake of Carbohydrate and Glucose.—Much has been written on this subject, but very little that is trustworthy. For this the apparent reason is that prior to the introduction of Bang's method in 1914 and the present more accurate method of Lewis and Benedict a determination involved the use of much more blood than is now required, with consequently but one or two tests in each case, whereas an examination is requisite every thirty minutes. Consequently the conclusions drawn from former experiments involve confusion.

Frank,[22] in 1911, asserted that in eight persons hyperglycemia of from 0.12 to 0.18 per cent. was found in the blood plasma after the intake of 100 gm. glucose in one hour's time, and that three persons showed a little sugar in the urine. Tachau[23] (1911), reported that no hyperglycemia was seen in one hour's time after a dose of 100 gm. sugar. Bing and B. Jakobsen[24] (Bang's micromethod) found hyperglycemia of 0.098 to 0.17 per cent. Among ten persons, after intake of glucose, two showed 50 per cent. and one showed 70 per cent. rise of blood sugar. The average rise after one hour was 36 per cent.,

19. Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, The Archives Int. Med., 1917, **20,** 761.

20. Foster: Am. Soc. Adv. Chem. Invest., 1917. Cited by Joslin (Footnote 4).

21. Jacobsen, Th. B.: Untersuchungen über den Einfluss veschiedener Nahrungsmittel auf den Blutzucker bei normalen, Zuckerkranken u. graviden Personen, Biochem. Ztschr., 1913, **56,** 471.

22. Frank, E.: Weitere Beitrage zur physiologie des Bluzuckers, Ztschr. f. physiol. Chem., 1911, **70,** 291.

23. Tachau, H.: Ueber alimentäre Hyperglykämie, Deutsch. Arch. f. klin. Med., 1911, **104,** 432.

24. Bing, H. J., and Jakobsen, B.: Blutuntersuchungen unter normalen u. einiger pathologirn Verhältnissen, Deutsch. Arch. f. klin. Med., 1914, **113,** 571.

and after two hours, only 11 per cent. These authors believe that a rise of more than 50 per cent. at the end of the first hour must be considered as pathologic.

Th. B. Jacobsen[25] (Bang's micromethod) found that 100 gm. glucose produces a rapid hyperglycemia which usually reaches its maximum in from fifteen to thirty minutes after the intake, keeps up one to three hours, and then falls to normal or even below. His experiments included fourteen persons whom he held to be normal. Among them six persons showed no urinary sugar, with blood sugar reaching from 0.12 to 0.16 per cent. Another group of eight persons showed sugar in the urine, with blood sugar of 0.17 to 0.227 per cent. However, the greatest amount excreted was only 1.38 gm. In the first group of six persons showing sugar, the hyperglycemia lasted about 1.75 hours; in the second group, about 2.5 hours. After 167 gm. bread (100 gm. carbohydrate), all fourteen persons reacted with a hyperglycemia (0.138 to 0.206 per cent.) which lasted from two to four hours, and six cases showed glycosuria (0.06 to 0.92 gm.). The only difference between the effect of dextrose and of starch was in the rapidity of the rise and fall of the blood sugar curve; that is, only a quantitative difference due to the difference in the rate of absorption. Jacobsen's results seem to be somewhat higher than normal, according to our present conception. There is a possibility that the use of the method was not accurate, with consequent high results, or that the experiments included persons of carbohydrate tolerance lower than normal.

Hopkins[25] (Bang's micromethod), in experiments with eight persons, found that the blood sugar reached its maximum (0.14 to 0.156 per cent.) in 30 minutes and lasted 2 hours. No urine examinations are reported. Graham[26] (Bang's micromethod), with three persons, noted that after 100 gm. glucose, the greatest rise of blood sugar was from 0.09 to 0.18 per cent., and the smallest was from 0.095 to 0.14 per cent. The maximum was usually reached in 20 minutes with return to the original level in from 1 to 1.5 hours. Cummings and Piness,[27] after the intake of 100 gm. glucose, found about a 50 per cent. rise during the first hour, with a drop of about one half of this during the second hour. In subjects having a low tolerance for sugar, the rise following the ingestion of 100 gm. glucose is distinctly higher than normal and the high level is well sustained up to the end of the second hour.

Hamman and Hirschman[19] (Lewis and Benedict's method) say that in the normal person, after the ingestion of 100 gm. glucose the blood sugar rises promptly to a level not exceeding 0.15 per cent., the high point is usually reached in about 30 minutes, and the whole reaction lasts from 1 to 2 hours, occasionally longer. They noted in many instances that where there is a considerable glycosuria, the excretion of sugar continues long after the blood sugar has fallen below the level at which it first appeared.

This latter fact—the continued excretion of sugar after the fall of blood sugar—may also be remarked in my case. Here, the maximum

25. Hopkins, A. R.: Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micromethod, Am. Jour. Med. Sc., 1915, **149,** 254.

26. Graham, G.: Variations in the Blood Sugar in Health, Jour. Physiol., 1915-1916, **1,** 285.

27. Cummings, R., and Piness, G.: A Study of Blood Sugar. Comparison of Tolerance for Glucose in Diabetic and Normal Subjects, THE ARCHIVES INT. MED., 1917, **19,** 777.

height and duration of the hyperglycemia after starch and glucose remain within the normal limit; the excreted sugar is below 1 gm., and there is no proportion between the glucose intake and the excreted sugar. Therefore, it is difficult to consider this case as a diabetes mellitus, but there is almost no doubt that it is a renal glycosuria, since the sugar excretion is due to the abnormally lowered threshold of the kidney, not to a pathologic hyperglycemia.

The Blood Sugar and the Renal Threshold of Diabetes.—The blood sugar of the diabetic is in higher concentration than normal. It is only in the mild form of the disease or under strict treatment that the blood sugar is normal. Following the administration of 100 gm. of glucose the rise in the blood sugar is greater than normal, and the rise is sustained longer than in normal men. Jacobsen[21] found in two cases of diabetes that an appreciable amount of sugar appeared in the urine, with sugar-freedom at the beginning of the experiment, and blood sugar below 0.15 per cent. He explained these facts on the ground that the diabetic excretes more sugar than normal at a certain level of blood sugar. It is also known that there is frequently a higher threshold for sugar in diabetics without evident renal lesions; some are free from glycosuria even when the blood sugar reaches 0.5 per cent.

According to Cummings and Piness,[27] in the mild form of diabetes, following the administration of 100 gm. glucose, the rise of blood sugar is longer sustained than normal, even to the end of the second hour. In a really or moderately severe case the blood sugar is higher two hours after intake of 100 gm. glucose than one hour after. Hamman and Hirschman[19] confirmed the finding that the hyperglycemia in mild diabetes is abnormal in definite respects: the blood sugar rose more slowly and reached its highest point later than normal; it also rose to a much higher level, all their three cases exceeding 0.2 per cent. Likewise, the fall of the blood sugar occurred much more slowly than in the normal, the whole reaction occupying from three to four hours. These authors believe that the *duration* of the hyperglycemia is a more important index of the severity of the alteration of carbohydrate metabolism than is the height of the hyperglycemia. Concerning the renal threshold in diabetes, they found that mild cases show a normal level. while moderately severe cases sometimes show a threshold below 0.15 per cent., but usually higher.

Graham,[28] in 1916, reported lower and higher thresholds for diabetes. His patient of lower threshold—a man of 32—in whom glycosuria had been detected five years previously, followed an unrestricted diet most of the time, with a sugar output of about 10 to 30 gm. daily. The blood sugar before a meal and

28. Graham, G.: Variations in the "Leak Point" in Diabetes Mellitus. I. A Low Level, Jour. Physiol., 1915, **49**, Proc. Physiol. Soc., p. 47.

after semi-starvation for twenty-four hours varied from 0.1 to 0.13 per cent., and sugar was always present in the urine. After 100 gm. dextrose the blood sugar rose 0.22 per cent. in one hour and had not quite fallen to its original level three hours later. The results in this case seem to indicate that the escape of sugar was due in some degree to permeability of the kidneys, or in other words, this case might represent a combination of renal glycosuria and true diabetes.

The Test of the Renal Function.—As it was clear that my case showed a lowered threshold for sugar, examinations of the renal function were made. McLean's[29] adaptation of the Ambard constant was employed for the determination of the excretion of urea and sodium chlorid.

TABLE 5.—The Relation of the Rate of Urea Excretion to Concentration in the Blood

Dec. 21, 1917 (10:20 a. m. to 11:32 a. m.); bleeding at 10:50; total urine, 168 c.c.

Weight, Kg.	Urea				NH_3	Acidity (Folin)
	Per Liter of Blood, Gm.	Per Liter of Urine, Gm.	Per 24 Hours, Gm.	Index	Per Liter of Urine, Gm.	$\frac{N}{10}$ Acid per Liter of Urine C.c.
51	0.244	9.05	30.41	270	0.229	55.8

Breakfast at 8 a. m.; bread, 40 gm.; butter, 20 gm.; 2 eggs; half grape fruit; 1 cup of tea.

TABLE 6.—The Relation of the Rate of Chlorid Excretion (Calculated as Sodium Chlorid) to Concentration in Plasma

Same morning.

Weight, Kg.	Sodium Chlorid					
	Per Liter of Urine, Gm.	Per 24 Hours, Gm.	Per Liter of Plasma			Threshold
			Calculated, Gm.	Actual, Gm.	Difference, Gm.	
51	7.8	26.2	6.21	6.25	+0.04	5.66

McLean has shown that the urea excretion index as an indicator of renal function is preferable to determinations of blood urea interpreted without reference to urea excretion. The tests were conducted as follows: breakfast at 8 a. m.; at 9:50, 200 gm. water drunk; at 10:20, urine passed; at 10:50, blood taken; at 11:32, that is, seventy-two minutes after the bladder was first emptied, the urine was collected, measured, and used for analysis. McLean's tables show that the normal concentration of urea in the blood varies from 0.2 to 0.5 gm. per liter. The normal urea index lies above 80, with an average of 120, based on 100 tests. Any index below 80 is considered abnormal, and the degree of impairment of functional ability or damage to the kidneys becomes greater as the index gets lower. An index above 300 may occur in healthy young persons with low blood urea; it may result from the washing out of urea with a high fluid output, or it may occur with "vascular hypersensitiveness" (Schlayer).

29. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man, Jour. Exper. Med., 1915, **22**, Nos. 2 and 3, pp. 212 and 366.

The urea index of my case is 270. This is due to the high fluid output, the rate of water excretion for twenty-four hours being 3,300 c.c. by calculation, while the daily volume of urine is always from 1,200 to 1,800 c.c. actually.

McLean has confirmed Ambard and Weill as to the law of chlorid excretion in relation to its blood concentration, and has found that normally the plasma chlorid varies from 5.62 to 6.25 gm. per liter according to the amount of salt ingested. There is a close agreement between the chlorid calculated in the plasma by Ambard and Weill's constant and that actually found.

The actual plasma sodium chlorid content in my case is 6.25, and the difference between the actual content and the calculated result is 0.04. Consequently, in this case the renal test shows no disturbance of kidney function according to the urea and chlorid excretion.

The Relation Between Diabetes and Nephritis.—It is well known clinically that when chronic nephritis occurs as a complication in diabetes, the kidney excretes less sugar than before and the sugar content in the urine is diminished. It is also known that hyperglycemia (without glycosuria) often occurs in cases of nephritis.

Myers and Bailey[30] lately reported hyperglycemia in nephritis and discussed the elevating influence of the nephritis generally accompanying advanced diabetes on the threshold of sugar excretion. According to Hopkins,[25] nephritic cases all furnish very high figures of blood sugar after feeding glucose, the duration of hyperglycemia lying between that of normal and of diabetic patients. Bing and B. Jakobsen,[24] in some cases of nephritis, after ingestion of glucose found an abnormal hyperglycemia but no alimentary glycosuria. Hamman and Hirschman[19] say that the renal threshold in nephritis is often above 0.2 per cent. In spite of the fact of the frequently high renal threshold in nephritis, however, there is sometimes a normal threshold in nephritis, and these authors found also a nephritis with a low threshold for glucose, in the neighborhood of 0.15 per cent.

As regards the kidney function in diabetes, Fitz[31] found that the urea index in the majority of the cases tended to be normal or abnormally high. In diabetes the plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill. McLean[29] found a lowering of the plasma chlorid in the majority of his observations in twenty-four cases of diabetes.

30. Myers, V. C., and Bailey, C. V.: The Lewis and Benedict Methods for the Estimation of Blood Sugar, with Some Observations Obtained in Disease, Jour. Biol. Chem., 1916, **24**, 147.

31. Fitz, R.: Observations on Kidney Function in Diabetes Mellitus, THE ARCHIVES INT. MED., 1917, **20**, 809.

REVIEW OF THE HITHERTO REPORTED CASES OF RENAL GLYCOSURIA

A search of the literature of renal glycosuria gives the following data:

1. Klemperer[1] (1896, Congress of Internal Medicine, Berlin) reported a case of old nephritis which showed 0.35 per cent. sugar in the urine with the normal figure for blood sugar; the intake of bread and 150 gm. glucose exerted no influence on the sugar content either of urine or blood; sugar in the whole blood was 0.175 per cent., which, according to our modern conception, must be considered as hyperglycemia. At the Congress of Internal Medicine in Wiesbaden in 1913, where the problem of renal glycosuria was again discussed, Klemperer's case was no longer recognized as a renal glycosuria.

2. Lüthje[5] reported a patient, aged 22, a merchant, with gonorrhea, cystitis, and probably ascending pyelonephritis. In the urine were found albumin and sugar below 1 per cent., reaching at the utmost 15 gm. a day. There was a constant excretion of sugar showing but very slight variation in the quantity despite great difference of carbohydrate intake per day. The single determination of sugar in the blood showed sugar as 0.055 per cent. in the whole blood. No mention was made, however, of the time or the relation to the diet, so that a conclusion concerning this case is consequently impossible. Lüthje claimed a relation between glycosuria and the nephritis because his case was apparently free from sugar *before* the nephritis, while sugar appeared in the urine shortly *after* the nephritis.

3. Bönniger[6] describes a patient, a man, aged 37, an alcoholic, who said that he had once shown urinary sugar of 2 per cent. After admission to the hospital he excreted sugar to the extent 0.2 per cent. on normal diet. During thirty-three days' observation in hospital, the percentage of sugar in the urine was remarkably constant in spite of great differences in carbohydrate intake, varying only between 0.1 and 0.5 per cent. The sugar content of the serum was 0.097 per cent.; of whole blood, 0.078 per cent. Occasionally when the urine contained 0.5 per cent. sugar, the blood sugar was 0.062 per cent. This patient, who was observed for six years, is in perfect health and still excretes a small amount of sugar. His son is also affected with renal glycosuria.

4. Weiland[7] makes a report of three cases which are not all, however, renal glycosuria.

5. Tachau[8] reports a patient, 21 years of age, a merchant, who developed gastro-enteritis after an excessive indulgence in fruit. The urine showed albumin, erythrocytes and casts (transient acute nephritis). The following schedule shows the results of experiments.

Diet	Days Observed	Urinary Glucose in 24 Hours, Gm.
Carbohydrate-free	4	0
Mixed (158 to 192 gm. C. H.).....	6	0
Mixed (124 to 412 gm. C. H.).....	15	1.1 to 6.0
Mixed plus 100 gm. dextrose.....	3	0.6 to 4.2

The percentage of sugar in the whole blood after fasting was from 0.085 to 0.086; one hour after 100 gm. glucose it was 0.07 to 0.109.

5. E. Frank[9] reports two cases: (*a*) a patient aged 51, who for four years had suffered from severe diarrhea of four weeks' duration, four or five times a year, without apparent cause. After the attacks glycosuria lasting about ten days was observed. Dextrose in the urine ranged from 0.05 to 0.5 per

cent.; sugar in the whole blood equaled 0.09 per cent.; in the plasma, 0.106 per cent.; (*b*) this patient suffered from a nervous complaint. Sugar in the urine was from 0.4 to 0.65 per cent.; in the whole blood, 0.08 per cent.; in the plasma, 0.08 per cent. In both cases, however, the time of the blood sugar determination and its relation to the diet were not shown, consequently, this report is incomplete. Frank's paper is valuable rather as a report of the literature and of his own experiments of renal glycosuria in animals under heavy-metal intoxication, as mercury, uranium and chrome. In these experiments he proved a true renal glycosuria. His exposition of increased renal permeability after poisoning with heavy metals, and also during pregnancy, suggests the existence of a clinically permanent renal glycosuria. Frank further emphasized the importance of estimating sugar in the plasma instead of in the whole blood.

7. In de Langen's[10] case, a patient of 22 years, sugar was always present in the urine, the quantity of excreted sugar varying between 4 and 19 gm. in twenty-four hours, and showing no proportional relations to the quantity of carbohydrate intake. After a carbohydrate-free diet there was a high content of sugar in the urine, while the smallest excretion of sugar was seen after a high carbohydrate intake. Intake of theobromin sodium salicylate (diuretin), which, according to some authors, influences sugar excretion, had no influence in this case. Blood sugar was determined in whole blood by Bang's method; there was hypoglycemia (0.054 to 0.073 per cent.); these results are, however, not decisive because the determination was not made until three hours after the meals instead of one or two hours, but they probably serve to rule out diabetes.

8. Galambos[11] reported a patient 50 years of age. During observation over a period of twenty-one days, while the carbohydrate content of the diet was between 50 and 354 gm. per day, the glycosuria varied between 66 and 198 gm. and the concentration of urinary dextrose between 2.6 and 7.4 per cent. Blood sugar during fasting showed 0.089 and 0.052 per cent.; one and a half hours after taking 100 gm. dextrose it was 0.17 per cent. After caffein, the urinary sugar was increased with the increase of urine volume. This case shows polyuria, polydipsia and acidosis, with much urinary sugar. The respiratory quotient was said to be 0.709 in fasting.

9. Lewis and Mosenthal[12] report the case of a man aged 29, who for the previous two or three years had had a tendency to increased frequency of urination during the day, but not at night. This condition had evidently been a pollakiuria rather than a polyuria, as the quantities voided apparently had not exceeded the normal. There were no diabetic symptoms. The patient excreted from 11 to 13 gm. sugar in twenty-four hours on "ward light diet." After the ingestion of 100 gm. glucose a hyperglycemia of 0.15 per cent. was evident within thirty-five minutes. Two hours and five minutes after the experiment was begun the blood sugar level returned to normal and subsequently became depressed below the normal level. The phenolsulphonephthalein test showed an excretion of 42 per cent. in two hours. Ambard's constant, determined at various times, was from 0.07 to 0.11 per cent. The kidneys were intact as far as physical and urinary signs were concerned; functional tests, however, revealed some impairment, as shown by a slightly diminished phenolsulphonephthalein excretion and an Ambard's constant barely within the upper normal figure.

10. Murlin and Niles[13] report a case of a man aged 20, with no diabetic heredity, who two years previously had furuncles, polyuria and thirst with loss of 10 pounds in one month. After admission to the hospital, sugar in the urine was between 19 and 34 gm. when the carbohydrate in the diet was between 15 and 100 gm. Examination for blood sugar at 11 a. m., five hours after break-

fast, revealed a normal percentage on several days. As this case was accompanied by diabetic symptoms, however, and as the blood sugar was not tested at the proper time, it is hard to classify it as renal glycosuria.

11. Strouse[16] had a patient aged 13 who felt perfectly well. With noncarbohydrate diet the urine showed a trace of sugar, not quantitatively measurable. After prolonged ingestion of carbohydrate, the urine showed the same trace of sugar, apparently no more and no less than was present when the patient was on a carbohydrate-free diet. Blood sugar was 0.04 per cent. one hour after a meal rich in carbohydrate.

DISCUSSION

There has been a gradual change from the former to our present conception of renal glycosuria. Klemperer[1] regarded this condition as a sort of anomaly of metabolism characterized by normal content of blood sugar with independence of sugar excretion from carbohydrate intake. Lüthje[5] and Naunyn[32] believed that a relation existed between renal glycosuria and nephritis. Naunyn[32] remarked a renal glycosuria occurring with granular nephritis; he reported three cases, but the lack of blood sugar determination leaves us uncertain whether there was hyperglycemia or hypoglycemia. Naunyn believes that nephritis influences the epithelia of the kidney to facilitate the excretion of sugar. This same author also reported glycosuria occurring after renal hemorrhage which had no apparent relation to the diet and which disappeared without any restriction of diet.

It is believed that glycosuria in pregnancy and in the puerperium is probably a renal process. Furthermore, Frank's[9] experiments confirm the work of many investigators concerning experimental renal glycosuria due to an increased permeability for sugar after poisoning with mercury, uranium, and chromate. Among the clinical cases of renal glycosuria already cited, the ones showing a previous affection of the kidney are those of Klemperer, Lüthje and Tachau. My patient also has a record of febrile albuminuria during typhoid fever ten years previously. But the general conception now is that the existence of kidney affection, that is, anatomic change of the kidney (morbus brightii and contracted kidney) is not necessary for the occurrence of renal glycosuria. The reasons for the permeability of the kidney to sugar are not yet known.

It has been shown that the blood sugar rises after meals (Bing and B. Jakobsen,[24] Th. B. Jacobsen,[21] Strouse[33]), and Joslin[4] says that the percentage of sugar in the blood of normal individuals rises promptly after meals and may reach 0.17 per cent. Accordingly, if the sugar threshold of the kidney is below the normal level, 0.17 to 0.18 per cent.,

32. Naunyn, B.: Der Diabetes mellitus, Wien, 1906, p. 136.

33. Strouse, S., Stein, I. F., and Wiseley, A.: The Accurate Clinical Study of Blood Sugar, Bull. Johns Hopkins Hosp., 1915, **26**, 211.

there must occur regularly after meals a glycosuria which lasts for a certain time and disappears spontaneously. It is pointed out by Hamman and Hirschman[19] that the lowered renal threshold may occur in otherwise normal individuals. They believe that a relation between the lowered renal threshold and renal glycosuria is obvious.

The intensity of the renal glycosuria will vary with the degree of the affection of the kidney, that is, its permeability to dextrose: (1) If the permeability is severely affected, with marked depression, urinary sugar will constantly appear even when the blood sugar content is very low. (2) When the renal permeability is but mildly affected, sugar will appear only at the high level of hyperglycemia of physiologic limit, and there will be no sugar in the urine with carbohydrate-free diet, because with that diet there occurs no high physiologic hyperglycemia. Under a diet rich in carbohydrate, the blood sugar will rise to the high level of physiologic hyperglycemia and sugar will appear in the urine. This high level of physiologic hyperglycemia is, in the normal subject with normal permeability of the kidney, a preglycosuric level.

Since we know that the blood sugar undergoes marked and rapid fluctuation after the ingestion of carbohydrate, and that urinary sugar has some relationship to hyperglycemia after meals, it is hardly possible to deny, to a certain extent, at least, the existence of a relationship of urinary sugar in renal glycosuria to the carbohydrate content of the diet. In the case under consideration there was no urinary sugar when the carbohydrate in the diet was below 34 gm., because the alimentary hyperglycemia occurring with that diet is under the threshold of the kidney for sugar. Blood sugar was highest after 200 gm. glucose, but the urinary glucose in that case was less than after 100 gm. glucose.

From the foregoing facts it is apparent that renal glycosuria may depend to a certain extent on the carbohydrate content of the diet. Therefore, a classification of this condition is necessary: (1) When the renal permeability is but slightly affected, glycosuria may not appear after a carbohydrate-poor diet; but, when it is severely affected, glycosuria will not disappear even after the entire witholding of carbohydrate from the diet. (2) Urinary sugar is not excreted proportionately to the increase and decrease of carbohydrate in the diet.

Von Noorden[2] remarks that in mild diabetes the urinary sugar is often independent of the carbohydrate intake. Therefore, too much attention must not be paid to the fact of the independence of urinary sugar to the carbohydrate in the diet.

The most important factor in the diagnosis of renal glycosuria is the presence of the normal level of the blood sugar when sugar appears in the urine.

Von Noorden[2] also says that renal glycosuria must be observed not a few weeks or months, but over a long period of time, since its progress is different from that of ordinary diabetes. Joslin[4] remarks the same thing. The author's case has been observed for five years, and the tolerance for carbohydrate is still the same and the subject is in good health.

Suggestions as to the Nature of Renal Glycosuria.—In the foregoing discussion I have tried to show that renal glycosuria may be defined according to the following characteristics:

1. Glycosuria occurs without *abnormal* hyperglycemia. Abnormal hyperglycemia, as previously stated, is entirely different from alimentary hyperglycemia of from 0.16 to 0.17 per cent., which is physiologic. Glycosuria occurs although the blood sugar is within this physiologic limit.

2. There is no disturbance of carbohydrate metabolism; the nature of renal glycosuria is entirely different from that of true diabetes mellitus, and consequently, there are clinically no diabetic symptoms.

3. Urinary glucose may or may not have some relationship to the carbohydrate in the diet, according to the degree of permeability of the kidney. In a mild case, sugar will disappear from the urine during a carbohydrate-free diet; glucose usually appears after rich carbohydrate intake.

4. During a long period of time no progressive increase of the abnormality occurs.

It is obvious that the term "renal diabetes" is not fitting for the characteristics just described, since the condition is not diabetes, but is "alimentary renal glycosuria."

Diagnosis of Renal Glycosuria.—Notwithstanding the fact that it is perfectly simple to observe that the lowering of the renal threshold results in the appearance of glucose in the urine without disturbance of intermediary carbohydrate metabolism, nevertheless, the question of renal glycosuria was left for a long time unsolved. The recent improved methods of blood sugar analysis have afforded the first opportunity of settling the question of blood sugar and especially of alimentary hyperglycemia. Now we know that when an individual shows sugar in the urine we must determine the blood sugar before we can make the diagnosis "diabetes," and furthermore, that in case of doubt, sugar must be determined in the plasma, because the renal threshold pertains most strictly to it. Examination of blood sugar is required not only once after fasting, but also at least twice every hour after a certain carbohydrate diet with resultant glycosuria. The elevation of the blood sugar and the renal threshold of the individual must

also be studied. Comparison of single blood sugar determinations is without value. By these means, just stated, we can learn whether the glycosuria is due to disturbance of carbohydrate metabolism or to the increased permeability of the kidney for sugar, according as the hyperglycemia present is within the physiologic limit or not. We learn at the same time the level of the renal threshold in the patient.

The glucose test, which must next be considered, consists in the study of the blood and urine of the patient beginning thirty minutes and continuing two or three hours following the intake of 100 gm. glucose with from 250 to 300 gm. water, after an over-night fast. This test shows the condition of carbohydrate assimilation of the individual. If the hyperglycemia still remains within the physiologic limit after the test, we may exclude diabetes mellitus and consider that the urinary sugar is due to the increased permeability of the kidney to sugar.

The one more important point is the observation of the case over a period of years, because, as remarked by von Noorden, there is a form of mild diabetes which shows a high tolerance for sugar in the early period of the disease. To differentiate renal glycosuria from this mild form of diabetes mellitus one must determine the course and watch the outcome.

Since renal glycosuria brings about no injury to the health or annoyance to the individual, it is possible that persons with a lowered sugar threshold may unconsciously for a long period excrete sugar in the urine after meals. The absence of symptoms may quite possibly conceal many cases of renal glycosuria which are not at present credited. It is also possible that some of the cases of the so-called mild diabetes in practice may belong to this form of glycosuria because the majority of them are diagnosed only by the examination of sugar in the urine, or, at most, by a single determination of blood sugar without relation to the preceding meal. An imperfect examination might easily diagnose as mild diabetes cases which in reality are renal glycosuria with a lowered threshold of the kidney for sugar and perfect carbohydrate metabolism.

Prognosis of Renal Glycosuria.—The present conception of renal glycosuria is that this condition is stationary; the glycosuria has no tendency to increase and the subject remains in good health. My case shows, during five years, only the same slightly depressed threshold and consequently only intermittent glycosuria after a meal rich in carbohydrate. Whether this condition will continue for a long period of time, say 10 or 20 years, or whether sooner or later a marked depression with constant excretion of sugar in the urine will occur, only the future can reveal.

Therapy of Renal Glycosuria.—It is believed at present that it is useless to keep to a strict diet in renal glycosuria. However, with the cases hitherto reported so few and the time of their observation so short, there is no surety that it is harmless to give carbohydrate and glucose in large amounts to persons with lowered kidney thresholds, since there is a chance that the depression might be thereby increased. The question is still open.

The author wishes to express his gratitude for the advice and criticism of Drs. F. M. Allen and D. D. Van Slyke throughout this work.

CONCERNING THE GASTRIC LESIONS OBSERVED IN EXPERIMENTAL BACTEREMIA *

J. W. McMEANS, M.D.
PITTSBURGH

The frequency with which hemorrhage and erosions of the stomach mucosa are found in infections and intoxications has led some investigators to suggest the possibility of such conditions having a certain influence in the production of gastric ulcer. Although these lesions do at times simulate the so-called peptic ulcer, still there is considerable doubt as to whether they ever lead to the round or chronic gastric ulcer as it is observed in the human. It is almost impossible to say that any one factor acts as an exciting or contributing cause in the development of a gastric ulcer. The many theories which have been advanced illustrate the diversity of opinion, and we are today probaby little more advanced in solving the problem than were the early writers. The ideas concerning the effect of an altered blood stream on the gastric mucosa, bringing about ulceration, as well as the part played by the central nervous system and local spasms of vessels themselves, are among several of the theories advanced by the early writers (Thorel[1]). Virchow was of the opinion that thrombosis and embolism of some parts of the coronary system had to do with the production of ulcer, while Openchowsky and v. Recklinghausen observed atheromatous lesions in the vessels of stomachs in which ulceration had occurred. According to Nauwerck[2] the alterations found in the blood vessels by the foregoing authors were secondary, as ulcers occurred in individuals in whom, he believed, infected food and an existing chronic gastritis were responsible for the conditon. In this connection Ruzicka[3] was of the opinion that the deleterious effect of the gastric juice on the mucosal cells is due to an aleration in the cells themselves and this author believed further that the superficial gastric cells are fairly easily injured by the gastric juice, while the deeper cells are more resistant to such insult. The mechanical theory was favored also by Stromeyer,[4] and particularly the injurious effect caused by the friction of food on the gastric mucosa. Thus it

* Submitted for publication April 20, 1918.

* From Cornell University, Surgical Division, and the Pathological Department of Bellevue Hospital.

1. Thorel: Lubarsch Ostertag, 1898, **5,** 142.
2. Nauwerck: Quoted by Thorel, Footnote 1.
3. Ruzicka: Wiener. med. Presse, 1897, **38,** 10.
4. Stromeyer: Ziegler's Beitr., 1912, **54,** 1.

would appear that ulcerations are developed by a local digestion of the mucosa which, as shown by Best,[5] are prevented under normal conditions by the presence of the antiferment in the cells.

The occurrence of lesions in the stomach following infections and intoxications has been repeatedly observed, with the result that erosions and purpuric spots have been described in the stomach in a variety of conditions. Nauwerck observed ulcers of the stomach in

Fig. 1.—Stomach; Rabbit 120; organism, *S. salvarius;* showing necrosis of folds with infiltration of polynuclear leukocytes and hemorrhage. There is extension of the inflammatory reaction into the muscularis mucosa.

scarlet fever, endocarditis and rheumatism, and has described these lesions as round or streaky erosions, with necrosis of the mucosa, not unlike those observed in multiple plugging of the capillaries by emboli. From this, Nauwerck designated a particular kind of ulcer in rheumatism. Among other workers, Widal and Meslay[6] also found ero-

5 Best: Verhandl. d. Deutsch. path. Gesellsch., 1913, **16,** 385.
6. Widal and Meslay: Quoted by Thorel, Lubarsch Ostertag, 1898, **5,** 142.

sions in the gastric mucosa following wound erysipelas, while Schimlinsky[7] described similar lesions in phlegmonous infection of the umbilical vein. In the so-called hemorrhagic infections, erosions and purpuric spots commonly occur in the stomach, and as Babes[8] has recorded, it would appear that no single specific organism is responsible for hemorrhagic disease. Thus, any organism which has a damaging effect on the blood vessels causing molecular destruction

Fig. 2.—Stomach; Rabbit 113; organism, *S. subacidus;* showing hemorrhage, necrosis and infiltration of polynuclear leukocytes which extend slightly into the mucosa.

of the walls may well be responsible for the disease. Likewise, the toxic products of bacteria are capable of producing not only purpuric conditions, but can also be the causal agent of excessive hemorrhages. Prominent among the authors who studied hemorrhagic disease was

7. Schimlinsky: Quoted by Thorel, Footnote 1.

8. Babes: Wien. med. Wchnschr., 1892, **34,** 1321; **35,** 1356; **36,** 36 and 1394; Idem. Zentralbl. f. Bakt. u. Parasitenk., 1891, **9,** 719.

Howard,[9] who described gastric and intestinal hemorrhage, in this condition, where capsulated gram-negative bacilli, streptococci and other organisms are directly concerned. This author concluded that hemorrhagic septicemia is, therefore, not to be regarded as a separate and distinct disease with definite and constant etiology, uniform anatomic lesions and clinical features, but rather as a toxemia attended

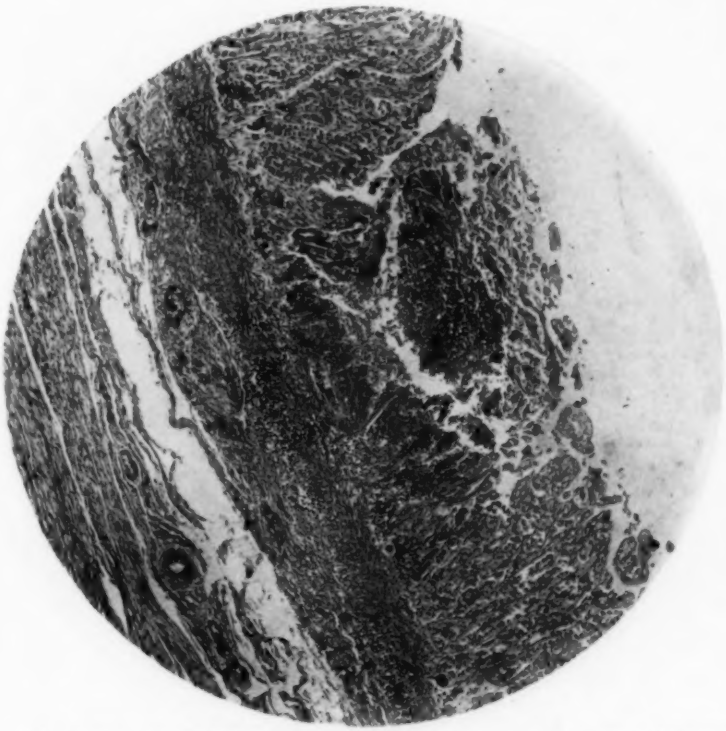


Fig. 3. Stomach; Rabbit 135; organism, *S. pyogenes;* showing ulceration and necrosis of mucosa with hemorrhage and leukocytes scattered through the necrotic material. The infiltration of leukocytes extended to the outer border of the submucosa but not beyond it.

by such marked injury to the blood vessels and to the blood as to cause extreme dilation of the vessels and hemorrhages with various harmful effects on the body cells. Similar alterations were recorded by Claisse[10] in pneumococcus septicemia.

9. Howard: Jour. Exper. Med., 1899, **4**, 149.
10. Claisse: Arch. de med. exper. et d'anat. path., 1891, **3**, 379.

Concerning ulcers of the stomach of this type, where it is maintained that the stomach is the only organ injured, Thorel made the very significant comment that ulcers due to infection are not found in otherwise sound people, but are seen in those persons suffering with a general infection. Oberndorfer[11] has described a type of hemorrhagic embolic enteritis which occurs in pyemia, while McCrae and

Fig. 4.—Stomach; Rabbit 69; spontaneous ulcer in pyloric ring.

Bardeen[12] have collected a series of cases from the literature which showed duodenal ulcer following extensive burns.

Just as gastric lesions have been found associated with a variety of conditions in human beings, so has it been the fortune of investigators to produce stomach lesions in experimental animals by diverse means. Bacteria have played their part in the work of several authors.

11. Oberndorfer: Verhandl. d. deutsch. path. Gesellsch., 1910, **14**, 159.
12. Bardeen: Johns Hopkins Hosp. Rep., 1898, **7**, 137.

notably Stewart and West[13] and Rosenow.[14] The first two workers succeeded in producing gastric erosions in five guinea-pigs which were injected intraperitoneally with a pathogenic strain of *B. Welchii*. They were also able to produce similar lesions in guinea-pigs injected

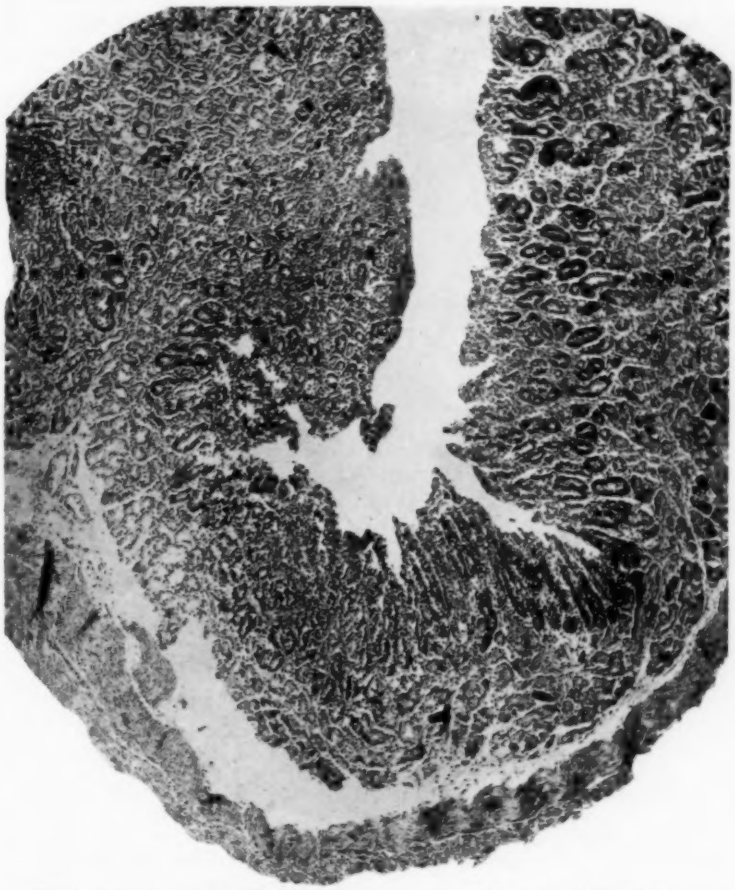


Fig. 5.—Duodenum; Rabbit 55; organism, *B. acidi lactici* and *Staphylococcus albus;* showing hemorrhage into mucosa with erosion of surface.

with acetic acid. In all instances these lesions were observed as erosions of the mucosa and submucosa with intact muscularis and serosa. Among the more recent studies of the bacteriologic production of

13. Stewart and West: Jour. Immunol., 1916, **1,** 187.
14. Rosenow: Jour. Infect. Dis., 1915, **17,** 219; idem., Jour. Am. Med. Asso., 1913, **61,** 1947.

gastric ulcer is that of Rosenow, who found gastric ulcer in 60 per cent. of animals injected with cultures of streptococci obtained from the tonsils of individuals suffering with gastric ulcer, while but 20 per cent. of the animals injected with his so-called "indifferent" strains of streptococci developed gastric ulcer. Ribbert[15] was able to produce a more advanced type of lesion by freezing the stomach wall with ethyl chlorid. After eight days, the muscularis showed marked erosion,

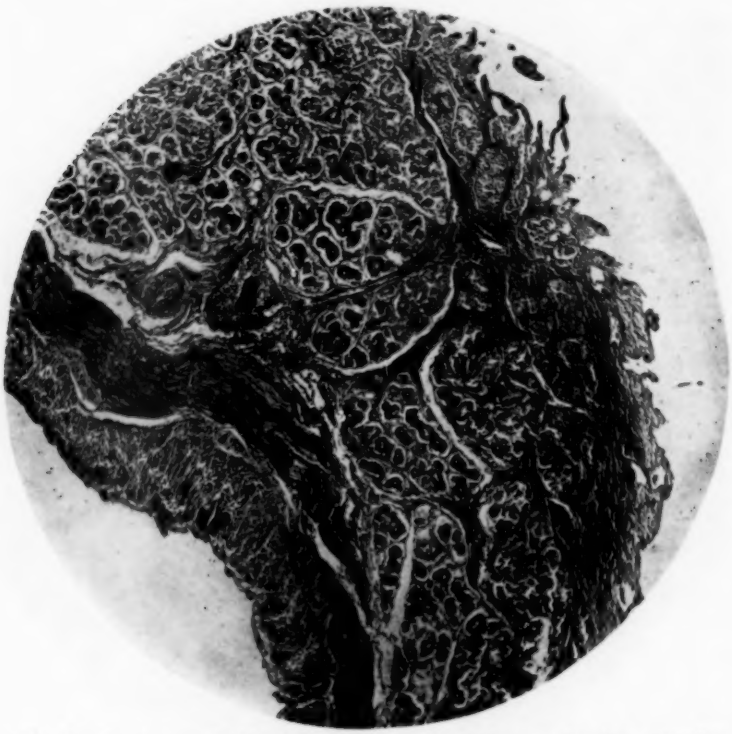


Fig. 6.—Duodenum; Rabbit 117; organism, *S. equinus;* showing extensive hemorrhage into the mucosa and about the glands in the submucosa.

with an exudate on the serosa and a cellular infiltration in the neighboring tissues. An area 2 cm. in diameter, representing the part frozen, was the only tissue affected. It would appear also that several of the endocrinous glands may at times be associated with gastric alterations. In this connection Mann[16] found gastric erosions in

15. Ribbert: Frank. Ztschr. f. Path., 1915, **16,** 343.
16. Mann: Jour. Exper. Med., 1916, **23,** 203.

adrenalectomized dogs and cats, while Finzi[17] observed the same condition following partial adrenalectomy in dogs and rabbits. Following the subcutaneous and intravenous injection of epineprin, Biedl[18] noted inflammatory and degenerative changes in animals not only at the site of injection, but also in distant organs, such as the mucous membrane

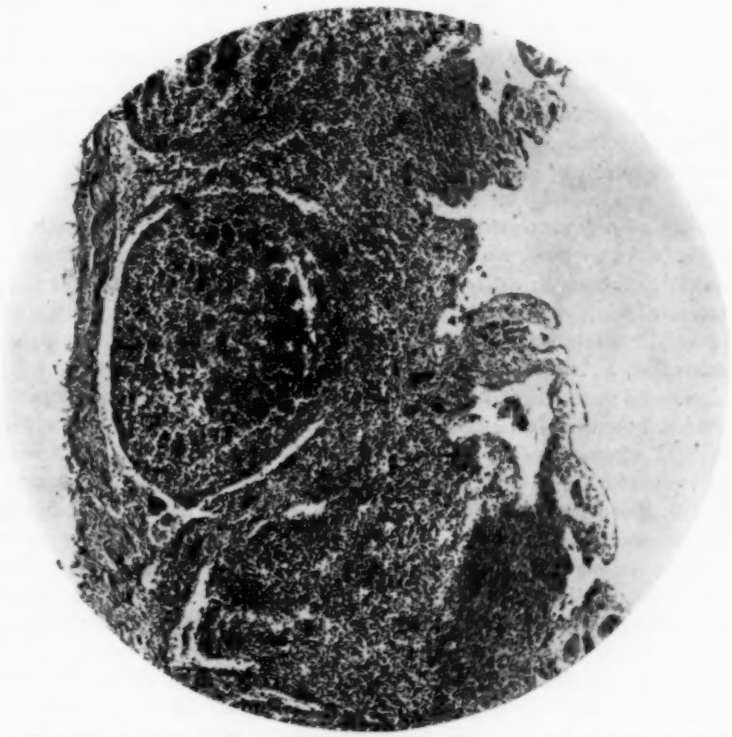


Fig. 7.—Peyer's patch; Rabbit 70; organism, *B. acidi lactici;* showing hemorrhage into Peyer's patch with erosion of surface.

and musculature of the stomach, intestines and urinary bladder. Similarly, Friedman[19] described gastric ulcers following the injection of thyroid extract and adrenalectomy and later observed the development of duodenal ulcers after the injection of epinephrin. In reference to this matter, Rosenau and Anderson[20] had previously pointed

17. Finzi: Virchows Arch., 1913, **214,** 413.
18. Biedl: Innere Secretion, 1913, **1,** 523.
19. Friedman: Jour. Med. Research, 1915, **32,** 95.
20. Rosenau and Anderson: Jour. Infect. Dis., 1907, **4,** 1.

out that gastric erosions are not infrequent in guinea-pigs killed with diphtheria toxin, a substance which causes marked adrenal lesions in these animals. The work of Bolton,[21] who succeeded in producing gastric ulcerations in guinea-pigs by inoculating them intraperitoneally with the serums of rabbits immunized with guinea-pig gastric mucosa or liver, is also interesting. From this brief review of the literature, it is evident that the etiology of gastric ulcer is still a much debated question.

During the course of our work on the hematogenous production of appendicitis we[22] were interested to find that the stomach frequently showed hemorrhages into the mucosal and submucosal tissues, as well as the development of erosions of these structures. No effort was made to select the organisms as far as their focal source was concerned and it was found that eighty-five of the 125 rabbits treated with a variety of organisms showed the described alterations in the stomach. Twenty-six of these animals received pure cultures of green streptococci, including *S. salivarius,* 19; *S. mitis,* 1; *S. fecalis,* 2; and *S. equinus,* 4. Twenty-eight animals were inoculated with cultures of hemolytic streptococci, including *S. pyogenes,* 19; *S. anginosus,* 3; *S. subacidus,* 5; and *S. infrequens,* 1. Eleven animals were treated with capsulated gram-negative bacilli, including *B. acidi lactici,* 9; *B. Friedländer,* 1; and *B. lactis aerogenes,* 1. Of the remaining animals which showed stomach lesions, 5 received *B. coli communis,* 4 *S. pyogenes* and pneumococcus, 3 *S. pyogenes* and *S. salivarius,* 3 *S. infrequens* and *B. Friedländer,* 3 staphylococci, 1; *S. salivarius* and *S. equinus* and 1 pneumococcus. Detailed data are shown in the table.

The lesions in the stomach varied from hemorrhage into the tissues of the mucosa and submucosa to ulceration of these structures. Even in the most severe reaction, the only alteration noted in the muscularis was an inflammatory infiltration, with but rarely any evidence of destruction of the inner muscle fibers. The lesions varied in size from that of a pinpoint to well defined areas 0.3 cm. to 0.5 cm. in diameter. In most cases the hemorrhages were discrete, although at times they were somewhat irregular in outline, with a tendency to become confluent when closely aggregated. These changes occurred in all parts of the stomach, although somewhat more frequently in the cardiac end. The erosions consisted for the most part of flat looking irregular patches, which, many times, were covered by a grayish slough situated on a deeply colored base. At times, however, larger areas of ulceration were seen. A rabbit injected with *Staphylococcus albus* and killed four days later showed a flattened, elongated erosion situated

21. Bolton: Jour. Path. and Bact., 1914, **19,** 258.
22. MacCallum: A Text Book of Pathology, Phila., 1917, p. 404.
23. McMeans: The Archives Int. Med., 1917, **19,** 709.

Lesions in Stomach and Other Organs

Organisms Injected	No. of Animals	Stomach	Appendix	Duodenum	Small Intestine	Heart		Joint	Muscle		Peri Art	Endocardium		Kidney	Thymus
						Hemorrhage	Infiltration		Hemorrhage	Infiltration		Hemorrhage	Infiltration		
S. pyogenes	25	19	14	7	5	4	9	14	2	2	2	15	2	3	9
S. subacidus	10	5	2	2	1	0	0	4	0	0	1	3	0	0	3
S. anginosus	3	3	1	1	1	0	1	0	1	0	1	2	0	1	2
S. infrequens	2	1	1	1	0	0	0	0	1	1	0	1	0	0	0
S. pyogenes—S. salivarius	5	3	3	2	3	0	0	4	1	0	2	2	0	0	3
S. pyogenes—pneumococcus	6	4	5	4	3	2	0	4	1	0	1	6	0	0	4
S. infrequens—B. Friedlander	4	3	3	2	4	0	0	2	0	0	1	4	1	0	3
S. salivarius	25	19	11	10	4	4	12	7	4	0	4	11	5	6	8
S. equinus	6	4	2	3	0	1	1	0	1	0	1	2	1	1	1
S. fecalis	2	2	0	2	0	0	0	0	0	0	0	1	0	0	1
S. mitis	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0
S. salivarius—S. equinus	1	1	0	0	0	0	0	0	0	0	0	1	1	0	0
Pneumococcus	1	1	0	0	0	0	0	0	0	0	1	1	0	0	1
B. Friedlander	1	1	1	1	1	0	0	0	0	0	0	1	0	0	0
B. acidi lactici	10	9	8	7	9	0	0	8	2	2	0	8	0	0	4
B. lactis aerogenes	1	1	0	1	1	0	0	1	0	0	1	1	0	0	1
B. coli communis	5	5	2	3	2	0	0	4	0	0	0	4	0	0	4
Staphylococcus	3	3	2	1	1	1	1	0	0	0	0	1	1	0	1
	111	85	55	47	35	12	24	48	13	5	15	65	12	11	45

Fourteen Animals Not Within the Groups That Presented Stomach Lesions

S. salivarius	6	0	2	3	0	0	1	0	1	0	0	2	1	0	1
S. pyogenes	3	0	1	0	0	0	0	0	0	0	0	0	0	0	0
S. mitis	2	0	1	1	1	0	0	0	0	0	0	0	1	0	0
Staphylococcus	3	0	3	2	2	0	1	0	0	0	0	1	1	0	1
Total	125	85	62	53	38	12	26	48	14	5	15	68	15	11	47

on the greater curvature near the cardiac opening. The base of the area was clean and light pink in color, with a number of dark hemorrhagic spots scattered through it. The borders of the ulcer were sharply defined.

Microscopically, varying degrees of reaction were observed. The most frequent alteration consisted of hemorrhage into the mucosa and a hyaline-like degeneration of the folds, with a slight infiltration of leukocytes and lymphocytes. The deep mucosa and remaining layers of the stomach wall were free. Again, the hemorrhage was more deeply situated in the region of the muscularis mucosa, and showed a loss of structure in the overlying mucosa, although at times the general hyaline outlines of this layer remained. In these areas there was a more marked infiltration of leukocytes, with, at times, many cocci distributed throughout the area. An animal injected with *S. pyogenes* illustrated the most severe type of reaction observed, and a microscopic description of these areas will serve to illustrate the third and less frequent degree of change. Sections of this animal's stomach showed an alteration which involved the layers down to the muscularis, but had left this coat unchanged. Over quite an extent, the mucosa was broken and eroded with islands of gland structures still to be seen between areas where the structure of the mucosa had been destroyed. In a large part of the area the mucosa was completely destroyed and replaced by an exudate of fibrin and leukocytes which extended into the muscularis in one place along the course of a lymphatic channel. The cells of the submucosa were swollen and increased in number. Along with the leukocytes, a number of eosinophils, lymphocytes and a few plasma cells were seen. Save for the large ulcerated areas, the reaction in the deeper tissues in other places had a patchy appearance not unlike areas of focal necrosis. A large amount of hemorrhage was distributed in the superficial tissues.

The frequency with which spontaneous ulcerations occur in the stomach of rabbits has not been definitely determined. Stewart and West,[12] however, found spontaneous ulcers in the stomachs of four guinea-pigs, and believed from their observations that the incidence was not higher than 1 in 25 or 30. In one of our rabbits, two ulcerations were found in the pyloric ring. These areas had a punched out character and were covered with a yellowish adherent stringy material. One was an elongated erosion measuring 0.6 by 0.2 cm. when held open by pressure from the serosal side. This area, however, appeared as an elongated slit running in the pyloric ring when the edges were at rest. The other ulcer formed a round punched out pit measuring 0.3 cm. in diameter, and was readily recognized without manipulation. Microscopically, there was complete absence of the mucosa, forming an eroded area covered by fibrin and necrotic debris, throughout which

leukocytes and lymphocytes were scattered. The base of the ulcer rested in the muscularis where there was a marked proliferation of connective tissue, within which bundles of muscle cells were seen. Large numbers of eosinophils and some lymphocytes infiltrated this tissue. The edges of the ulcer were not undermined. In some respects, the ulceration just described resembles the more advanced lesions observed at times in animals which survived the intravenous inoculation for twenty-four to forty-eight hours. In the latter animals, however, the erosion did not extend as deeply into the wall as the spontaneous type described, and there was no attempt at healing as observed in the latter type. Thus, with a definite case of spontaneous ulceration at hand, it would be somewhat difficult to entirely exclude those advanced erosions not associated with hemorrhage from this class. Further, the presence of a single ulceration of this type without other evidence of injury to the gastric mucosa should be looked on skeptically as being caused by the treatment given the animal. Of first importance is the fact that deep involvements of the wall are uncommonly noted in this type of experiment in that the process is essentially one of hemorrhage followed by superficial erosion.

The changes noted in the duodenum were very similar to those observed in the remainder of the gastro-intestinal tract, save for the fact that the erosions were not as marked as those found in the stomach. The entire gastro-intestinal tract was commonly the seat of hemorrhage and presented this picture in the following order: stomach, appendix, duodenum, small intestine, cecum and large bowel. Hemorrhages occurred in the duodenum fifty-three times following the injection into rabbits of a variety of organisms that were in no instance selected with a view to demonstrate localization in this organ. Even in the most severe form, the reaction in the intestinal tract did not present more than a slight erosion of the mucosa. Frequently, however, there were quite extensive hemorrhages into the submucosa and Peyer's patches.

Whether or not these lesions can be compared with peptic or round ulcer as it is observed in the human is a much debated question. Lesions similar to those which occur in rabbits in this type of experiment have been described in human hemorrhagic disease by a large number of writers. Furthermore, they have also agreed that there is no single organism which can be named as the exciting cause of hemorrhagic disease. Regarding stomach lesions of the type in question, Thorel was of the opinion that they were never found in otherwise healthy individuals, but always in those individuals suffering with a general infection. It is on these points that we wish to lay particular emphasis. We have succeeded in producing hemorrhage and erosions of the gastric mucosa in rabbits by treating them with a variety of

organisms, and in all there were other evidences of a general infection. Hemorrhages were the prominent feature in other organs of the body, although, just as in the stomach, an inflammatory reaction occurred not infrequently. The ultimate outcome of these lesions is difficult to determine, in that one is not afforded the opportunity of studying them at varying periods. It seems, however, that these lesions disappear spontaneously in the majority of cases, and there is no definite evidence to support the idea that they burrow deeply into the stomach wall, in that all of the lesions noted were superficial in type, and as a rule did not extend beyond the inner layers of the submucosa. The stomach mucosa, no doubt, has a great power for healing, and it would appear that other tissues besides the mucosa are injured in the production of chronic ulcer of the stomach, as it is observed in the human. MacCallum[22] has removed a large part of the stomach mucosa of dogs, and on later examination found the mucosa entirely intact. This observation agrees with that of Best, who found that healthy mucosal cells contain a substance that guards them against digestion. In this case, healing would occur from surrounding healthy cells by extension in a manner similar to that observed in other epithelial covered surfaces. Further, Nauwerck found that the cells underlying the gastric mucosa are very resistant to the action of the gastric juice. The digestion of the small areas of mucosa in the stomach deprived of nutrition by an underlying hemorrhage occurs rapidly, due to the action of the gastric juice, and these small pits are frequently found filled with a chocolate colored blood. With the removal of the impaired tissue by the action of the gastric juice, the surrounding healthy cells undertake the task of repair. From our own observations, and the evidence which we are able to gather from the literature, we do not believe that these lesions represent the initial stage in the development of a gastric ulcer as it is observed in man. The finding of what appeared to be a spontaneous gastric ulcer in a rabbit supports this view, in that the experimental lesions and the spontaneous lesions were very dissimilar. Such lesions cannot be justly compared with the usual type of gastric ulcer observed in man, in that the strenuous methods employed exert a far more widespread influence on the tissues of animals than is ever found in humans suffering with gastric ulcer. They more nearly approach the appearance of the human gastric lesions which occur during the course of a general infection, and are but one of the several manifestations of such a disease. Furthermore, we cannot support the view of elective affinity expressed by Rosenow, in that we have observed with equal frequency hemorrhage and erosions of the stomach of rabbits following the injection of various organisms obtained from indifferent sources.

AUTHOR'S NOTE: This work was carried out under the direction of Dr. John A. Hartwell, to whom I am much indebted for advice and assistance.

BOOK REVIEW

DIFFERENTIAL DIAGNOSIS. Presented through an analysis of 317 cases, by Richard C. Cabot, M.D., Assistant Professor of Clinical Medicine, Harvard University Medical School, Volume 2, Edition 2. Octavo of 709 pages, 254 illustrations. Philadelphia and London: W. B. Saunders Company, 1918. Cloth, $6.00 net.

In the present volume of this popular work Dr. Cabot presents in his clear and forceful manner a series of cases illustrative of several important and common signs and symptoms encountered in clinical medicine. The book is apparently the outgrowth of a smaller manual so successfully employed by the author in case teaching in the Harvard Medical School and case reports used in clinical pathologic conferences conducted at the Massachusetts General Hospital.

The signs and symptoms, which include abdominal and other tumors, vertigo, diarrhea, dyspepsia, hematemesis, glands, blood in the stools, swelling of the face, hemoptysis, edema of the legs, frequent micturition and polyuria, fainting, hoarseness, pallor, swelling of the arm, delirium, palpitation and arrhythmia, tremor, ascites and abdominal enlargement, form the subjects of the several chapters. The records of the Massachusetts General Hospital have been exhaustively searched for clinical conditions in which the subjects of the various chapters were prominent features and the results tabulated in an imposing manner in the order of the frequency of their occurrence in the various diseases. The tables appear at the beginning of each section and are accompanied by a brief discussion of the importance of the particular sign or symptom in question in disease entities. The discussions are characteristically clear and concise and leave no doubt in the reader's mind as to the author's opinion on the topics taken up. His remarks on the significance of dyspepsia are particularly good and should be valuable as an aid in the differential diagnosis of stomach disorders.

Throughout the book there is a tendency to be dogmatic and to give undue emphasis to the value of statistical methods in clinical medicine. One receives the impression from reading the discussions and case reports that diagnosis in medicine usually is not difficult. Most diagnostic problems may be divided into three groups: one group in which the diagnosis is easy; a second group in which the condition is most certainly one of two or three things, and it is in this group that the most skill is required to make an accurate diagnosis. In this group it is necessary to bring together all the possible available data for careful consideration in the light of experience and knowledge. The author rightly emphasizes the importance of keeping in mind the presenting symptoms in these cases. It is, however, dangerous to rely too much on the relative frequency of the occurrence of any particular symptom to influence one in diagnosis. The general picture is necessary. In the third group are placed those cases in which the evidence is insufficient to make a definite diagnosis. The cases are numerous, varied, well chosen and admirably presented for the most part.

One feels at times that completeness has been sacrificed to clearness and brevity.

On page 43 Dr. Cabot expresses a certain skepticism as to the ability of the "scientifically trained" physician to evaluate adequately subtle histories. In

reply to this, attention may be called to the statement on page 28, Case 1, where the Abderhalden test is spoken of as a distinct aid in the diagnosis of pregnancy. The Abderhalden test has some years since been proved by the "scientifically trained" physician to be unreliable as a diagnostic of pregnancy.

The book is most attractively assembled, has frequent illustrations, with good cuts, allowing of no confusion concerning the physical signs, and is particularly free from typographical errors. It fills a very distinct and important place in third and fourth year teaching as a book for collateral reading in connection with this particular work.

CONTENTS OF VOLUME XXI

APRIL, 1918. NUMBER 4

The Significance of Variations in the Blood Picture in Pneumonia. Edward Rhoads, M.D., Philadelphia, and Thomas Cullen, M.D., Baltimore, Md.

Experimental Observations on the Production of Pneumococcic Empyema and Its Treatment by Intrapleural Injections of Antipneumococcic Serum. Alexander Cannon, M.D., and Walter G. Phillips, M.D., Philadelphia.

Empyema Thoracis and Cardiac Complications. Joseph A. Capps, M.D., Chicago.

Empyema Thoracis. Peter Irving, M.D., New York.

A Study of the Epidemiology of Acute Poliomyelitis, Based on Observations in Pittsburgh and Mount Kisco, New York, in 1916. Simon Flexner, M.D., and Paul A. Lewis, M.D., Philadelphia.

The Pituitary Gland in Poliomyelitis. The Condition of the Sella Turcica. Samuel Kopetzky, M.D., and J. M. Stewart, M.D., Bronxville, N. Y.

The Intravenous Serum Treatment of Epidemic Cerebrospinal Meningitis. Major W. W. Harris, M.D., Camp Jackson, S. C.

Book Reviews. Journals of the Practitioner. Medicine by Eminent Authors, M.D.

MAY, 1918. NUMBER 5

Experiments on the Vasomotor Action of Blood Platelets. Theodore C. Janeway, M.D., Henry [illegible], M.A., and E. K. Dunham, M.D., New York.

Relation Between the Platelet Count of the Blood and Its Vasoconstrictor Action After Operation. E. Hirsch, M.D., Chicago.

Clinical Calorimetry. Paper 25. The Effect of Some Drugs on Heat Production. [illegible], M.D., Ph.D., and [illegible], M.D., New York.

Clinical Calorimetry. Paper 26. Metabolism Studies on Cases of Pernicious Anemia and Leukemia. [illegible], M.D., and [illegible], M.D., New York.

Clinical Calorimetry. Paper 27. Metabolism Studies on Cases of Chronic Arthritis and Fibrositis. [illegible], M.D., and [illegible], M.D., New York.

The Influence of Exercise and Fasting upon the Metabolism of Obesity. [illegible], M.D., and [illegible], M.D., New York.

The Influence of Exercise upon the Metabolism of Diabetes. [illegible], M.D., and [illegible], M.D., New York.

The Nutritive Assistance of C. G. Salzer, Assistant Professor of Physiology, Rush Medical College, Chicago.

A Further Study of Ethylhydrocuprein (Optochin) in the Treatment of Acute Lobar Pneumonia. Henry J. Hirsch, M.D., Chicago.

Acute Chronic, M.D., New York.

Circulatory Reactions to Exercise During Convalescence from Infectious Diseases. Samuel Hyman, M.D., New York.

The Occurrence of Mucoid-like Substance in the Red Blood Corpuscles. James Kennaway, Assistant Physiological Chemist, Guy's Hospital, London.

JUNE, 1918. NUMBER 6

[illegible], M.D., Vienna.

[illegible], M.D., Chicago.

[illegible], M.D., Philadelphia.

[illegible], M.D., Minneapolis.

Concern-Antitoxic Potency in Sera Precipitated by Certain Salts. Francis G. Blake, M.D., and [illegible], M.D., New Haven, Conn.

Brain Changes Associated with Pregnancy. Asaph C. Berry, M.D., Wellman, M.D., Minneapolis.

Book Reviews.

Index to Volume XXI.